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THE GENESIS OF CARCINOMA OF THE FALLOPIAN TUBE IN HYPERPLASTIC SALPINGITIS, WITH REPORT OF A CASE AND A TABLE OF TWENTY-ONE REPORTED CASES.

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Among theoretical conceptions of pathological processes to which disease is attributable are certain ideas that have at their inception the distinctness of a silhouette. With the advancement of knowledge, the margins of certain notions lose their definiteness and we find various processes uniting insensibly at their boundaries. The idea that necrosis means death of tissue remains firmly planted, but the exact limitation of its import is considerably blurred when the process of gradual death is screened behind the caption of atrophy. Any attempt deserves approval that has for its object the segregation and classification of morbid processes that lie in the boundary zone. It seems, however, that as time advances the narrow distance now separating the process of tissue hyperplasia from that concerned in the development of benign tumors will not be increased. Lubarsch,[1] after commenting on the close connection between tumors and infectious processes, notes this difficulty in the following words: "Suchte man daher nach anderen un-

[1] Ergebnisse d. allg. Path. u. path. Anat., 1895, ii, p. 290, Wiesbaden.

terschiedenen Kriterien, so machte sich eine weitere Schwierigkeit, die Abgrenzung gegenüber die Hyperplasie bemerkbar." Still, it is evident that if a process of questionable character midway between tumor and hyperplasia can be traced to an inflammatory origin, its position is no longer in doubt. It must of necessity be considered as hyperplasia or the meaning of the word tumor will require modification. In lesions of such uncertain species, in which the inflammatory origin is manifested by simply one of the inflammatory phenomena, viz., that of proliferation, the question seems surmountable in only one way—to admit without further discussion the existence of a firm bond uniting them. Such a solution of the problem is rendered easy by finding lesions which represent all transition stages from one process to another. An example of this kind is reported by W. W. Van Arsdale:[2] a growth developed on the upper right arm two days after several blows received during a sparring bout. A fluctuating swelling that increased the circumference of the arm 10 cm. was present two days after injury; one month later the mass had decreased to one-third its former size, but it had become hard and immovable. Two months after the injury, a growth 9 cm. in length and 3 cm. in its other diameters was chiseled from between the biceps and branchialis anticus; it was found to possess an outer shell of bone 1.5 cm. thick, the periosteum being closely adherent to its exterior, and a cavity filled with dark partially coagulated blood; its outer wall was true bone and its cavity devoid of bone-marrow proper; its inner wall was porous vascular bone.

It seems reasonably certain that in this case the clot of a subperiosteal hæmorrhage became ossified at least in its outer part. According to Klebs,[3] the process of bone-formation in this "Ossifying hæmatoma" would serve as an example of hyperplasia; for, he states, the line between hyperplasia and tumor-growth may be determined to some extent by the preponderance of the former in scars and granulation tissue and its proneness to spontaneously disappear. The growth would be inflammatory in origin, for the unabsorbed blood would excite an inflammation in the surrounding parts (Cohnheim).[4] According to Lubarsch,[5] the apparently autonomous hyperplastic growths almost without exception follow inflammatory excitants. Notwithstanding these opinions, it is unreasonable to suppose that had ossification been allowed to continue throughout the entire coagulum, that the mass of new bone would ever have disappeared spontaneously; there would have resulted an osteoma—a benign tumor. Surgeons are well acquainted with the permanent character of the bony hyperplasia which occurs in a luxuriant callus and the osteomas that develop in the biceps and pectoral muscles from the kick of a gun (Tillmanns).

Another instance of lesions which represent transitions between hyperplasia and benign tumor is furnished by multiple adenomata of the liver. In proof of their mediate position is the fact that equally good authorities are arranged on opposite sides: Weichselbaum, Rindfleisch, Chiari and Kretz classify the condition with simple hyperplasia; Lubarsch, Thoma, Ponfick and Eppinger with adenomata. Orth[6] seriously considers the question of tumors arising from multiple nodular hyperplasia of the liver, and Schmieden,[7] in a recent review of the connection which exists between these lesions, declares that a sharp division between adenoma and hyperplasia in the liver cannot be made. He claims to have seen, as Van Heukelon did before him, the transition forms between hypertrophied liver cells and tumor cells. The relationship between hyperplastic processes and tumor is more important when it has to do with cells that possess great powers to proliferate and regenerate, *e. g.*, surface epithelium and the epithelium of superficial glands. In discussing this subject Birch-Hirschfeld[8] makes the statement that such atypical hyperplastic growths show in the excess of their regeneration certain points of similarity to tumors, and it may be accepted that they may become changed into tumors; he also states[9] that the possible occurrence of growths which represent transition stages between hyperplasia and tumor can not be excluded.

The effect of a productive inflammation or inflammatory hyperplasia upon mucous linings is either a diffuse and uniform thickening or the formation of the isolated polypoid outgrowths. As the gross appearances change from a diffuse process to dispersed or widely scattered growths, the likelihood of the inflammatory origin lessens, for the conception of a tumor is connected with the local limitation of its early growth (Thoma). But to this there are exceptions, for "the inflammatory new growths, which are due to atypical proliferation of epithelium, tend to form either single, tumor-like protuberant growths or multiple growths over a considerable surface" (Birch-Hirshfeld).

The confusion which attends the word papilloma is no more attributable to its diversity of structure than to the question of its proper position in regard to tumors and the hyperplastic inflammations. Birch-Hirschfeld[10] states that in mucous membranes a diffuse or circumscribed polypoid thickening may result from chronic catarrhal inflammation; also, that in the nose[11] combinations of papilloma and hyperplasia of the mucosa occur. Klebs[12] uses the polypi of the stomach to illustrate the effect of hyperplastic inflammation in the production of papilloma. In the statement by Orth[13] concerning the papillomata of the Fallopian tube, that it is difficult to determine with certainty to what extent they are caused by inflammatory growths of the folds of the mucosa, we have further evidence of the confusion.

[2] Ann. Surg., 1893, xviii, p. 8, Phil.
[3] Die allg. Pathologie, etc., ii, p. 491, 1889, Jena.
[4] Vorlesungen über allg. Pathologie, p. 393, 1882, Berl.
[5] L. c., p. 297.
[6] Lehrbuch der spec. path. Anatomie, i, p. 957, 1897, Berl.
[7] Arch. f. path. Anat. (etc.), clix, p. 290, 1900, Berl.
[8] Grundriss der allg. Pathologie, p. 144, 1892, Leipzig.
[9] Lehrbuch der path. Anat., i, p. 180, 1896, Leipzig.
[10] L. c., p. 137.
[11] Lehrbuch der path. Anat., ii, p. 450, 1894, Leipzig.
[12] L. c., p. 615.
[13] Lehrbuch der spec. path. Anat., ii, p. 539, 1889, Berl.

Such uncertainty of classification leads naturally to the use of terms which are devised to bridge over the difficulty. Such a title, alluding both to the process of hyperplasia and to the admixture with tumor, is used by Hauser[14] in his report of a case of "Polyposis intestinalis adenomatosa." In this case there were disseminated polypi consisting largely of atypical epithelial growths not only throughout the intestinal canal but also in the stomach. Hauser refers to three other similar cases. Petrow[15] has added another in which there were numerous single or clustered, large and small polypous growths in the stomach and the entire intestinal canal, together with every evidence of a severe chronic inflammation in the mucous coats involved.

Quénu and Landel[16] have recently collected 42 cases in which the large intestine was the seat of a more or less extensive polypous hyperplasia. From the frequent history of diarrhœa, these authors believe that the process has its origin in inflammatory conditions, and this opinion is reached after a thoughtful consideration of the possibility that the intestinal disturbances might be secondary to the multiple adenomata. In a previous article by the same authors[17] there is even less doubt displayed respecting the identity of pedunculated adenomata of the rectum with hyperplastic processes, for the statement is made that "they are more or less directly dependent upon an inflammatory reaction."

Sklifossowsky,[18] after describing two benign papillary tumors in the mucous lining of the stomach, states that they originated from a hyperplasia of the mucous coat due to long-standing irritation; he likens them to the knob-like projections of the *état mamelonné*. His interest in these growths was largely due to the fact that all transitions were found in them between the diffuse thickening of gastritis proliferans and the tumors described.

Further evidence is not necessary to illustrate the fact that hyperplastic processes in the mucous lining of the gastro-intestinal tract, like those of the liver, are closely allied to the processes of tumor-development; or that there are certain interposed lesions which might be accepted as proof of the continuity of processes having as their onset chronic inflammation, and, as their termination, tumor-growth. The analogy will be more complete with the demonstration of cases such as are hinted at by Birch-Hirschfeld[19] in the following proposition: "It is probable, but not proven, that certain forms of primary carcinoma of the liver may have their origin in a further atypical development of such liver adenomata." The fact that the hyperplasia of the gastro-intestinal mucosa has, as its end product, the evolution of *malignant* neoplasms, leaves no room for controversy such as has been noted with regard to multiple adenomata and nodular hyperplasia of the liver.

In 42 cases gathered by Quénu and Landel of polypous hyperplasia of the colon, there were 20 in which a carcinoma of the colon was also present. In the series of Hauser,[20] of carcinoma of the colon, five were associated with more or less extensive "polyposis," and in the stomach the same author reports one case in which the process was combined. (Case 25, p. 208.)

One of the cases of benign tumor of the gastric mucosa which Sklifossowsky so positively ranks with the inflammatory hyperplasias, possessed at the same time a carcinoma, which was sufficiently interesting, on account of the early changes it showed, for Israel to report it under the title "Ueber die ersten Anfänge des Magenkrebs."[21] Also, in the case of Petrow, of diffuse gastro-intestinal polypous hyperplasia, death took place from invagination and spontaneous rupture at two places, where the growth had a similarity to adenocarcinoma.

To substantiate the view that the polypous growth occurs first and that the production of tumor follows, the following citations will suffice:

Orth,[22] in considering similar growths in the Fallopian tube, writes as follows: "Among the recently reported cases of papillary new growths are some which may be correctly deemed benign and others which are malignant; from the great similarity of these to one another it is safe to accept the view that there is at least a danger of cancerous transformation. Hauser, in the report mentioned of a case of Polyposis intestinalis adenomatosa, claims (p. 446) that one must admit that the multiple warty growths have developed first and that these later underwent a carcinomatous change. Cullen,[23] after referring to the opinion of Lubarsch, that a benign tumor is never changed into a malignant one, says: "Case 4,262, which I have recently had the opportunity of studying, shows beyond a doubt that such a possibility exists." The case in question was that of a polypous adenoma of the uterine mucosa.

The investigations on inflammatory hyperplasia with tumor-formation in certain regions have been repeated by Stoerk[24] in the urinary tract. He describes a case of papillomatosis of the urinary bladder, ureter and pelvis, of the right kidney, and was able to find only two similar cases in the literature. He considers the process as an unusual form of chronic inflammatory hyperplasia, and compares it with Gastritis proliferans. More commonly the chronic inflammation in the urinary passages terminates in a hyperplasia associated with the formation of cysts. That certain cases should display both features of the process is not sur-

[14] Deutsches Arch. f. klin. Med., lv, p. 429, 1895, Leipzig.

[15] Bolnitsch. gas. Botkina, 1896, St. Petersburg. From the summary of Russian literature by Maximow and Korowin, Ergebnisse d. allg. Path. u. path. Anat., Lubarsch and Ostertag, v, p. 735, 1898, Wiesbaden.

[16] Les polyadénomes du gros intestine. Rev. de Chir., xix, p. 465, 1899, Paris.

[17] Rev. de gynéc. et de chir. abd., ii, p. 484, 1898, Paris.

[18] Arch. f. path. Anat. (etc.), cliii, p. 130, 1898, Berl.

[19] L. c., p. 743.

[20] Das Cylinderepithel-carcinom des Magens und des Dickdarms, p. 261, 1890, Jena.

[21] Berl. klin. Wchnschr., xxvii, p. 649, 1890.

[22] L. c., p. 539.

[23] Cancer of the Uterus, etc., p. 355, 1900, N. Y.

[24] Beit. z. path. Anat. u. z. allg. Path., xxvi, p. 367, 1899, Jena.

prising. Litten[25] has described "Ureteritis chronica cystica polyposa." Cahen[26] has one case, and to this Stoerk adds three more, in which the hyperplasia of the mucous lining of the bladder was accompanied by carcinoma. Rehn[27] makes the interesting statement that in the majority of tumors of the bladder a substance in solution in the urine causes the tumor-growth by its chemical irritation; he has observed three cases in which tumors of the bladder occurred in men employed in the manufacture of aniline dyes. Stoerk is inclined to lay strong emphasis upon gonorrhœa as an etiological factor, and Kaufmann[28] has described the occurrence of multiple polypi in the ureter from the passage through it of faeces from a fistulous connection between the pelvis of the kidney and the duodenum. As an example of the question which so constantly recurs—tumor or inflammation—and serving as an illustration of the apparent necessity to separate these conditions, the following quotation will answer:[29] "The condition described might be classed both as chronic cystitis and as tumor. . . . I am inclined to look upon the process as a chronic cystitis." This is in concluding an article on Cystitis Papillomatosa, where the cystoscopic examination left the observer in doubt. In the recent work by Cullen on Cancer of the Uterus, there is abundant evidence that a diffuse polypous hyperplasia of the uterine mucosa occurs and that this condition may be combined with carcinoma. The illustrations on pages 514 and 516 show its gross anatomy; some participation of the epithelium in the process is evident, since in many places it was many layers in depth in both cases, notwithstanding that no karyokinetic figures were found. Case 3,452 (p. 323) of "adenocarcinoma of the anterior cervical lip; commencing adenocarcinoma of the posterior lip, apparently independent of the former; papillary outgrowths of the uterine mucosa, with suspicion of commencing adenocarcinoma of the body of the uterus," is a striking analogy with the polypous hyperplasia with carcinomatous transformation observed in the intestinal mucosa and the urinary tract. Perhaps the best example of polypous hyperplasia described by Cullen is Case 6,659 (p. 401). Occurring in a young woman, aged 30, this author describes "a very unusual polypoid condition," in which "the mucosa, as a whole, presents a most unusual picture, consisting of large polyp-like masses springing from all parts and completely filling the enlarged cavity." Histologically, "one of the chief features is the preservation of the lumina of the glands; few, if any, nuclear figures are to be made out," and "the uterine muscle has not been penetrated by the growth; in fact, at some points there still remains a small amount of normal mucosa separating the growth from the muscle." There had been no recurrence of tumor 11 months after the removal of the uterus. The diagnosis was adenocarcinoma. There is but little doubt, so far as one can judge from the report, that in this case the process was one of diffuse polypous hyperplasia which, so far as the examination shows, had not at the time of removal undergone carcinomatous change. That such a change would have occurred, had it been undisturbed, might be inferred from the continuity of process which has been shown so far to exist between the polypous hyperplasia and carcinoma.

But it is especially concerning tumors of the Fallopian tube that confusion has arisen; there has been quite a general failure to recognize that a diffuse hyperplastic inflammation is possible—a process which is strictly analogous to the polypous hyperplasia of other mucous surfaces—and that in certain typical examples it is as distinct from tumor-growth as gastritis proliferans is from carcinoma of the stomach. Part of the confusion is no doubt due to the fact that hyperplasia is so frequently combined with sacto-salpinx. Slavyanski[30] has recognized this fact, as is established by the frequency with which he uses the term *sacto-salpinx papillomatosa*, although he does not clearly distinguish between papilloma as a tumor and polypous hyperplasia due to chronic inflammation. He states that "with occlusion of the abdominal end, the tube appears larger, aside from the papilloma; products of the secretion both from the covering of the tumor and the diseased mucosa accumulate in the tube; thus sacto-salpinx becomes sacto-salpinx papillomatosa (p. 112)." Numerous investigations in lower animals have proven that when the outer end of the tube is closed a retention cyst is the result.[31] Undoubtedly in many cases the inflammatory process which leads to the hyperplasia of the mucous lining of the tube causes the closure of the abdominal end. As a typical example, the case reported by Doléris and Macrez[32] will answer. He removed from a woman, aged 37, a growth of the right tube which was adherent to the liver and measured 20 by 30 cm. It consisted of a sac filled with grumous, viscid, yellowish fluid; its walls were 5 to 10 mm. and the lining was beset with pin-head to pea-sized papillary growths, which, on microscopic examination, consisted of villi with rarely more than one layer of epithelial cells as a covering. This is the second growth of this sort removed by Doléris; the other, in 1891,[33] being the first observed in France. The woman was 28 years old; the growth was in the right tube and the inner one-fourth of the sacto-salpinx contained no papillary growths. Clark has reported a similar case[34] of a cystic growth of the Fallopian tube 12 by 12 cm., or one-half the size of a man's head, in which the inner surface was studded with thick papillary growths except at one point, where the

[25] Arch. f. path. Anat. (etc.), lxvi, p. 139, 1876, Berl.
[26] Arch. f. path. Anat. (etc.), cxiii p. 468, 1888, Berl.
[27] Verhandl. d. deutsch. Gesellsch. f. Chir., xxiv, s. 240, 1895, Berl.
[28] Cited by Stoerk.
[29] F. Bierhoff, The Medical News, lxxvi, p. 810, 1900, Phil.
[30] Special Pathology and Therapy of the Diseases of Women, vol. ii, Diseases of the Fallopian Tubes and Ovaries (Russian), 1897, St. Petersburg.
[31] C. Gebhard: Pathologische Anatomie der weiblichen Sexualorgane, pp. 436–7, 1899, Leipzig; also: Ergebnisse d. allg. Path. u. path. Anat., 1898, v, 741 (work of Sadkowsky), Wiesbaden.
[32] La Gynecologie, iii, p. 289, 1898, Paris.
[33] Nouv. Archiv. d'Obstet. et de Gynec., vi, p. 11, 1891, Paris.
[34] Johns Hopkins Hospital Bulletin, ix, p. 163, 1898.

surface for an area the size of a palm was smooth. The wall of this cyst was thin; the warty growths were largely made up of connective tissue, and the epithelial covering of these was uniformly single-layered. Although Clark ascribes the process to inflammation, it is reported as the seventh instance of papilloma of the Fallopian tube. Another instance first reported on account of the concurrent appendicitis[35] was shown on later examination of the sac,[36] which was as large as a fœtal head, to contain the inner part of the tube as a curved cord on its outer surface. The lining of the sac was beset with small growths covered with epithelium; the crypts between the growths extended outward so as to give to the section an appearance not unlike an adenoma. The condition described in this case might be considered as analogous to cystitis cystica of Stoerk and others, which led Aschoff to search for glands in the urinary tracts of newly born infants. It is essentially the same process—a hyperplasia of the lining (sacto-salpinx villosa et pseudo-follicularis). Both this case and that of Montprofit and Pilliet[37] are included by Macrez in the table of benign papillary tumors of the tube; in concluding the case above mentioned, the following interesting statement is made:

"L'origine irritative de ces productions dans la trompe ne doit pas surprendre, puisque l'on voit que dans les viscères comme le foie, le rein, la capsule surrénale, etc., les formations adénomateuses coexistent avec la sclérose et paraissent être un des modes de réaction des cellules parenchymateuses aux irritations qui amènent l'épaississement du tissu conjonctive."

The second case of papilloma reported by Doran[38] was double-sided; the right tube contained over a pint of fluid, the left a smaller amount. Both contained papillary growths which Doran describes as warts "similar in principle to those found in other structures, namely, overgrown papillæ, the result of continued irritation."

It is certainly of doubtful propriety to consider these growths, so clearly the products of an inflammatory action, as "papilloma." Sacto-salpinx papillomatosa might be altered with advantage to Sacto-salpinx polyposa, for the condition is one of diffuse polypous hyperplasia associated with the formation of a retention cyst and not one of tumor-growth. By some observers the diffuse villous hyperplasia associated with sacto-salpinx has been reported as carcinoma. W. L. Jakobson[39] has reported a case in which the papillary growths almost filled the sac. Although the epithelium had not proliferated so as to invade the musculature of the tube, and notwithstanding that there were no metastatic growths, the condition of the tube was diagnosed carcinoma by both Jakobson and Petroff, who made the histological examination. In the case reported by Hofbauer[40] both tubes were closed externally, but retention cysts were absent. The lining of the right tube, in which the changes were more advanced, possessed small miliary and larger growths, some as large as two beans. From the gross changes and from the careful description of the histologic structure, this might also be considered as polypous salpingitis, did not the record point so well to tuberculous salpingitis. The sac in the case operated by Leopold and described by Fearne[41] measured 5 cm. in diameter and occupied the infundibulum and ampulla of the tube. It was filled with a soft vascular papillary growth. The lining folds have hypertrophied, branched, and then, according to Fearne, undergone malignant transformation. The muscle fibers had disappeared by atrophy and a firm connective-tissue wall had so successfully limited the process that there were no metastatic growths and the patient was well 1½ years later.[42] The case reported by Sänger and Barth,[43] over which they hesitated long before concluding that it was one of carcinoma, which diagnosis has constituted one of the principal factors of the present confusion, was one in which the tubal mucosa was thickened so that it resembled the cerebral convolutions in miniature. The accompanying illustration, showing the macroscopic appearance of the lining, resembles greatly the mammillated appearance of the stomach in gastritis proliferans. This thickening affected the outer one-half of the tube uniformly; there were numerous nuclear figures in the epithelial cells which covered the villi in a single layer, and largely from this histologic similarity with "Adenoma malignum" of Ruge and Veit, these authors concluded finally that it also was carcinoma. The diffuse character of the process in this case, and the uniformity with which the tubal mucosa was involved, point to a hyperplasia similar to that seen in other mucous coats—to a condition resulting from inflammatory reaction with excessive proliferation or the early disappearance of all other changes but proliferation—a process which Adami, following Klebs, refers to as "neoplastic hyperplasia," and which Hauser, as before noted, connects with tumors by the term "polyposis adenomatosa."

It does not always happen that the outer end of the tube becomes closed by the inflammatory process; the subsequent invasion of the adjacent peritoneum, by papillary or warty growths, however, is no proof that the process is one of tumor-growth; for, in condyloma acuminata an exactly similar process occurs—extension of a hyperplastic inflammation by direct continuity of surface. The classical case of Doran[44] is of this nature. The outer part of the right tube was dilated and filled with cauliflower-like growths; these were formed by villi covered by a single layer of epithelium of which some cells were ciliated. There was also an enormous ascites and pleural effusions which required frequent

[35] Bull. Soc. Anat. de Par., 1897, xi, n. s., p. 518.

[36] P. Macrez: Des Tumeurs papillaires de la Trompe de Fallope, p. 61, 1899, Paris.

[37] Bull. Soc. Anat. de Par., 1893, vii, p. 505.

[38] Tr. Path. Soc., 1888, xxxix, p. 200, London.

[39] J. akush. i jensk. boliez., xii, p. 29, 1898, St. Petersb.

[40] Arch. f. Gynäkol., lv, p. 316, 1898, Berl.

[41] Über primäre Tubencarcinom. Geburtshülfe u. Gynäkologie, ii, p. 337, 1895, Leipzig.

[42] Tr. Obstet. Soc. (London), 1898, xl, p. 202.

[43] Die Krankheiten der Elleiter, A. Martin, p. 253, 1895. Berl.

[44] Tr. Path. Soc. (London), 1880, xxxi, p. 174; Idem., 1882, xxxiii Supplementary Reports, p. 49.

tapping; although it was impossible to remove the entire growth, no recurrence had taken place 16 years after the operation." It is more reasonable to believe this case to be one of hyperplastic salpingitis than of tumor. Doran, in his original report, likened it to the venereal condylomas and to the inflammatory polypi of the tubal mucosa described by Rokitansky and Hennig.

Another condition has been described by Schirschoff [45] as papilloma. It is that of a single pedunculated tumor which arose from the lining of the tube 5 mm. inside the fimbriæ; the abdominal os was wide and gaping. The growth was 5 cm. in length and made up of a cluster of smaller masses. The exact pathologic position this growth should occupy as regards the Fallopian tube will always be in doubt, since there is but slight mention of the large (wt. 410 g.) papillary cystoma which was situated just below the outer end of the tube. In other cases such localized growths have been catalogued as carcinoma. Stroganoff [46] has described a single pedunculated growth which arose from the mucosa by a pedicle 1 cm. in diameter. The tube containing it was closed externally and held about 50 ccm. of the usual serohemorrhagic fluid. The structure of this growth was such that a diagnosis was made of "carcinoma cylindro cellulare." There is no mention of regional invasion, glandular involvement or recurrence; the woman was 39 years old. Tuffier [47] found in a tube, which was closed externally, pear-shaped and as large as a fœtal head, a dark, soft and friable mass which was at first supposed to be free; in examining it a narrow pedicle was found. The lining of the sac containing this growth was, for the greater part, smooth and devoid of epithelium. The examination of this growth alone, which, like that of Strogonoff, was largely necrotic, led to a diagnosis of carcinoma (epithelioma).

Falk [48] also described a localized growth as carcinoma. On the left side the tube formed a sac that contained a sanious, semi-purulent fluid and in its outer part gelatinous cysts; the sac formed by the right tube was as large as a child's head. It contained a similar fluid, free, grayish, villous masses, and on the posterior wall springing from the mucosa, a growth the size of a walnut; this contained gland-liko structures, and from its histologic resemblance to the case of Sänger and Barth, a diagnosis of carcinoma was reached. It is obvious that in this instance the chronic inflammation on one side caused sacto-salpinx with hyperplasia of the lining and the formation of pseudocysts; on the opposite side, sacto-salpinx with the production of a localized growth. In cases of this nature, the effort to separate tumor and hyperplasia meets, in the localized nature of the growth, an obstacle which is at present insuperable. If there occur in such localized growths evidences of the multiplication of cells—nuclear figures—or if alterations are found in the morphology and staining reactions of the cells which would indicate that they have not reached an adult type, the process is certainly more like tumor than like hyperplasia. But between hyperplasia and carcinoma there is a considerable gap. Hauser, after describing the multiplication of the glands in the polypi of the intestine, makes the statement [49] that it should not be understood that all such growths are of necessity precursors of carcinoma. With the article of Schmieden [50] there are portrayed atypical karyokinetic figures in the liver cells which form the adenomata. In short, it seems to me that the case described by Falk does not correspond to carcinoma so much as it does to a benign and localized growth; here it is necessary to recur to a proposition made earlier—that it is doubtful whether the narrow distance now separating hyperplasia from benign tumor will be increased. It is reasonable to believe that there should occur in the lining of the Fallopian tube regenerative processes, similar to those of glandular organs and structures possessing glands, the products of which are closely allied to adenomata.

The foregoing considerations demonstrate the imperceptible transition of hyperplastic processes of the tubal mucosa—belonging properly to the salpingitides—into those of true tumor growth; and that these may terminate in the production of benign tumors. The literature of tubal tumors also contains abundant evidence that the transition of villous hyperplasia into growths that at least possess some indications of malignancy is an equally gradual one. The tumors demonstrated by Kaltenbach as double-sided tubal carcinoma [52] were later elaborately described as papillomata.[53] Carcinoma is positively excluded in the following words: "Aber nirgends lässt sich doch ein Anhaltspunkt für eine wirkliche Carcinombildung finden, auch da nicht, wo die Neubildung mehr einen parenchymatösen Character hat, und von einer Zerstörung des bindegewebigen Papillärkörpers durch eingedrungene Epithelmassen ist nichts zu sehen." Notwithstanding this statement, there was a recurrence within 18 months.[54] In Eckhardt's [55] case the cyst formed by the dilated outer portion of the tube had small elevations on its external surface which, on microscopic examination, were found to consist of solid outgrowths of epithelium. In a report by Fabricius,[56] the left tube was removed and the growth that it contained pronounced papilloma by Paltauf. The right adnexa appeared normal and were left in place. Five months later a large growth occupied the right side of the pelvis, and masses removed from where the left tube had been amputated were declared by Paltauf to be carci-

[45] A System of Gynecology, by many writers, edited by T. C. Allbutt and W. S. Playfair: Diseases of the Fallopian Tube by Alban Doran, p. 806, 1897, London.

[46] Bolnitsch. gas. Botkina., Nos. 42–44, 1898.

[47] Collection of works in Obstetrics and Gynecology, dedicated to Prof. K. F. Slavyanski (Russian), p. 227, 1894, St. Petersburg.

[48] Ann. de Gynéc. et d'Obst., 1894, xlii, p. 203, Paris.

[49] Berl. klin. Wchnsch., 1898, xxxv, p. 554.

[50] L. c., p. 447.

[51] L. c.

[52] Centralbl. f. Gynäk., xvi, p. 357, 1889.

[53] Ztsch. f. Geburtsh. u. Gynäk., 1889, xvi, p. 364, Stuttg.

[54] Doran Tr. Obstet. Soc., 1898, xl, p. 200.

[55] Archiv f. Gynäk., 1897, liii, p. 183, Berl.

[56] Wien. klin. Wchnsch., 1899, xii, p. 1230.

noma. In the instance chronicled by Michnoff,[57] the folds of the lining of the left tube were thickened by many strata of epithelium and the muscular layers in some places were invaded through their entire thickness. The condition in the right tube considered by Michnoff as papilloma corresponds very well with sacto-salpinx villosa; the epithelium, rarely more than a single layer, covered papillary growths 1 cm. tall, and these filled the canal near the outer end of the tube; the os abdominale was closed and a cyst had formed there the size of a small hen's egg. In a case reported by Kretz as papilloma,[58] sacs had formed on both sides that exhibited externally small, white, soft, flat nodules. By the study of serial sections, these were found to be produced by the growth outward of the crypts between villi; the diverticula produced in this manner usually possessed a single layer of tall epithelium; where the epithelium was in two or three layers the cells were shorter and nuclei more spherical. Such cystic formations were found within the lymph channels.

Although it is not within the scope of this article to insist on the glandular character of the epithelial tubal tumors, certain facts may be pointed out. It is obvious that the five cases above cited as examples of growths that were removed during the transition between hyperplasia and tumor are very similar to proliferating papillary cystoma of the ovary. This similarity with ovarian tumors has been dwelt upon by many writers. Gebhard[59] compares them with uterine carcinoma in the following words: "Obwohl ich selbst, wie eingangs erwähnt, keine eigene Erfahrungen über das Tubencarcinom besitze, so bin ich doch bei der Durchsicht der in der Litteratur niedergelegten Beschreibungen des mikroskopischen Verhaltens dieser Geschwulst zur überzeugung gekommen, dass dieselbe histologisch durchaus mit dem malignen Adenom u. Adenocarcinom des Uteruskörpers auf eine Stufe zu stellen ist."

The classification of tubal carcinomata into purely papillary and papillo-alveolar by Sänger and Barth[60] is but a makeshift for adenocarcinoma; as Cullen says,[61] concerning adenocarcinoma of the uterus, "I am strongly of the opinion that where the papillary arrangement is most marked, the growth has started in the surface epithelium; whereas it seems probable that when the gland-like arrangement is more pronounced, the process has started first in the glands. The simpler plan would be to consider all these merely as variations in one disease." Slavyanski[62] would limit the term adenocarcinoma to the latter form of Sänger and Barth. He separates them into two forms—carcinoma papillomatosa villosum and carcinoma cylindrocellulare seu adenocarcinoma.

From the description of the following case it may be seen that the view of Cullen relative to the two methods of growth in the adenocarcinoma of the uterus is equally applicable to tubal carcinomata; that there is a disposition to grow towards the lumen in the form of branching villi as well as outward into the muscular coat as sacs, diverticula or alveoli, and that these methods of growth are part of the same process.[63]

I received, June 22, 1899, from Dr. Henry P. Newman of Chicago, a tumor which was removed by him at the West Side Hospital. I am deeply indebted to him for the opportunity to examine it. The following abstract of the clinical history was also obtained from him:

Mrs. F., age 47, admitted to the West Side Hospital June 20th; in her early married life she had two miscarriages at the third and fourth months of pregnancy respectively. Subsequently, she gave birth at term to a child, which is now 21 years of age; delivery was instrumental and severe. Since then she has been unable to carry a child beyond the third or fourth month of pregnancy. In spite of many miscarriages she has enjoyed a fair degree of health until two years ago, when menstruation became painful. The pain was referred to the sides and lower abdomen; it began just before the flow and continued during the entire period; there was also experienced general weakness and exhaustion on slight exertion. One year ago she first noticed a protrusion from the vagina which she took to be the womb; this has gradually enlarged, becoming more prominent after standing, straining, and coughing. It has never been painful, but has proved annoying in walking or sitting from its large size. There has also been an enlargement of the abdomen until it is now as large as a pregnancy at full term. She complains of a frontal headache; she has a fair digestion; there is no constipation or urinary trouble, but there is a constant leucorrhœa and the discharge is often streaked with blood.

Operation.—Incision in the median line of the abdomen 8 cm. long; over two gallons of ascitic fluid escaped; the left tube was very much enlarged and thickened; the ovary was not involved. The tube was excised close to the cornu of the uterus. The right adnexa appeared normal; wound closed with catgut and silk in layers. The protruding culde-sac of Douglas was then opened from below, emptied of its contents – a large amount of ascitic fluid – and the vaginal fornix, which was so redundant as to protrude at the vulva, was removed and its edges closed with catgut sutures. The uterus was curetted and packed with iodoform gauze. There was nothing removed from the uterus which led to any suspicion of its containing a neoplasm. The patient, though fractious and unmanageable, made an uninterrupted recovery, leaving the hospital at the end of the third week.

Macroscopical Appearance.

The mass consists simply of the left Fallopian tube. Its uterine end tapers abruptly and the abdominal end is the seat of an exuberant, cauliflower-like growth of new tissue which appears to have burst forth from the tube (Fig. 1).

[57] Meditsina, iii, p. 181, 1891, St. Petersb.
[58] Wien. klin. Wchnsch., 1894, vii, p. 572.
[59] L. c., p. 455.
[60] L. c., p. 272.
[61] L. c., p. 360.
[62] L. c., p. 116.
[63] This case was briefly reported at the Chicago Gynecological Society, December 15, 1899, by Dr. Newman and myself.

The tube forms a small U-shaped bend, the convexity of which is upward. The middle of this convolution measures 1.5 cm. in diameter. It then bends downward and becomes greatly dilated. Its external surface is covered with a smooth, glistening, unbroken serous membrane which contains many circularly arranged blood-vessels. All signs of fimbriæ at the outer end have disappeared. At the external end is an abrupt termination of the smooth serous covering which is overrun with tissue grown out of the abdominal ostium. This new tissue consists in part of small, smooth nodules which vary from .6 and .8 to 1.5 and 2 cm. in diameter and of shaggy, rough tissue between the rounded parts. This outgrowth is spread over more of the under surface of the tube than elsewhere; it is very friable. The ovary and its ligament form a pedunculated appendage to the tumor mass and is small as compared to the large tube (Fig. 2). The length of the growth is 13.5 cm. The ovary contains a large corpus luteum; the external surface is smooth. Just in front of the tubo-ovarian ligament is a small accessory tube measuring 28 mm., springing directly from the serous covering of the main tube; its stalk is 1 mm. in diameter; its outer end is dilated (Fig. 1). The weight of the entire mass is 250 grammes. The tumor was hardened entire, and without cutting, in Mueller's fluid and formalin (4 per cent), except a small, irregular mass detached from the external end; this was hardened in strong alcohol (95 per cent). When the hardening was completed the tube was sectioned through its long axis. The center was found occupied by a soft material of a gray color; it filled the canal, and extends between the projecting masses of tissue which fringe the lining (Fig. 3). The muscular coats are thin, but the mucosa by its proliferation has invaded the necrotic content of the tube for a distance which averages 1 cm. in all parts of the tube. The proliferating lining is dotted over with grayish, necrotic débris. The greatest accumulation of this material has occurred in the middle of the tube where it measures 2 cm. in diameter; at this point the remaining 5 cm. of the diameter of the tube is occupied mainly by the proliferating mucous membrane. The muscular and fibroserous coats measure from 1 to 3 mm. in thickness. At the uterine end of the tube there is a large amount of necrotic material in the lumen and but slight proliferation of the lining; at the abdominal end this condition is reversed.

Microscopic Appearance.

Sections were cut from points along the whole length of the tube and stained by various methods. The structure is essentially the same in all portions. Set upon the muscular coats, which are thin, are many papillary or villous growths. They are usually tenuous stalks of connective tissue covered with epithelium (Fig. 1), which branches and rebranches to form a tassellated lining (Fig. 4). The epithelium consists of many strata, of which only the deeper layers have a columnar type. The nuclei are oval and irregular and do not stain very strongly. The absence of a nuclear membrane and the arrangement of the chromatin in certain nuclei betokens poorly preserved karyokinetic figures. This assumption is made certain by finding, after some search, certain masses of chromatin which are plate-shaped and, in other cells, the double plates of metakinesis. Such nuclei in process of division are quite numerous; they are as abundant in the outer strata as in the inner. In sections stained after the iron-hæmatoxylin method, these nuclei in various stages of division form black masses. In some of the dividing nuclei, in spite of the unfavorable fixation, the centrosomes and the pointed ends of the groups of achromatic threads may be seen. There are no more irregularities in these dividing nuclei than might be accounted for by the hardening process. The layers of cells often number ten to twenty and in the outer parts of the tumor near the abdominal end they are even more numerous. The many-layered appearance of the epithelium is not due to the thickness or obliquity of the section, for in very thin sections cut in paraffin and not more than one cell in thickness, at least four to six layers are present, and this is true for regions where the outer layers have undergone considerable necrosis, where, in fact, the tips of papillæ are buried in necrotic débris. In no place are any single rows of epithelium upon a basement membrane found, such as occurs in the normal folds of the tubal mucosa. With low powers of the microscope the epithelial character of these cells is not clearly evident because of the large size of the nuclei as compared with the scanty amount of protoplasm surrounding them. Even with the immersion objective some appear to possess very little protoplasm. The nuclei alone average about seven mikrons in diameter when they are circular; the nuclei of the columnar cells measure in their long diameter ten to eleven mikrons. Exceptionally very large nuclei may be found which measure 15 to 20 mikrons in diameter. In practically every nucleus of the resting cells there may be found small oval bodies colored a pale green, with the hæmatoxylin and eosin staining; with the iron and hæmatoxylin and considerable differentiation, these bodies are much darker. Very rarely two occur in the same nucleus; they are undoubtedly nucleoli; the peculiarity consists in their large size. Very often they equal in diameter one-third or one-fourth of the diameter of the nucleus; exceptionally they occupy one-third of the entire nucleus. The columnar shape of the cells close to the stroma is manifested more by the shape of the nucleus than by the cell body; in this region the nuclei are more closely arranged in palisade form.

On the edges of these villous growths where the epithelium is in contact with the necrotic material, and in places where the edges of papillæ are in contact, the epithelial cells have undergone degenerative changes. Here occur occasional nuclei, usually smaller, in which the chromatin is collected in a few granules which stain intensely with nuclear dyes, and such granules commonly festoon the inner margin of the nuclear membrane or form a few crescent-shaped masses on its lining. Such nuclei may appear devoid of cell bodies. More frequently the necrosis has resulted in shrunken and

FIG. 1.—Tubal carcinoma—anterior surface—natural size.
a.—Accessory tube.

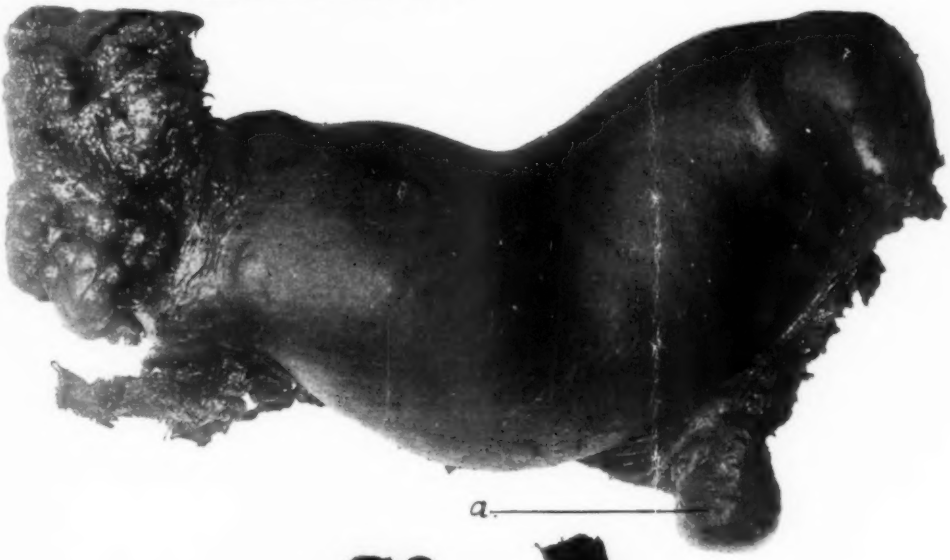

FIG. 2.—Tubal carcinoma—posterior surface—natural size.
a.—Ovary.

FIG. 3.—Tubal carcinoma sectioned longitudinally (three-fourths of natural size).
a.—Uterine end.
b.—Muscular wall.
c.—Necrotic tissue.
d.—Papillary growth of the lining toward the lumen of the tube.

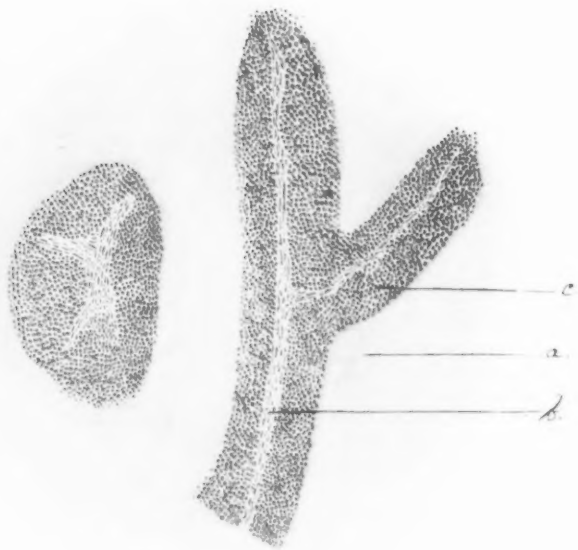

FIG. 4.—Villi that have been sectioned longitudinally and transversely; from the more central part of the growth.

a.—Necrotic tissue.

b.—Connective-tissue stalk.

c.—Epithelial cells in many strata.

FIG. 6.—"Inverting type" of proliferation. The epithelium between the papillary growths has proliferated outward toward the muscular wall.

a.—Necrotic tissue.

b.—Stroma.

c.—Epithelium.

d.—Masses of epithelium lining cavities that have not been opened in this section.

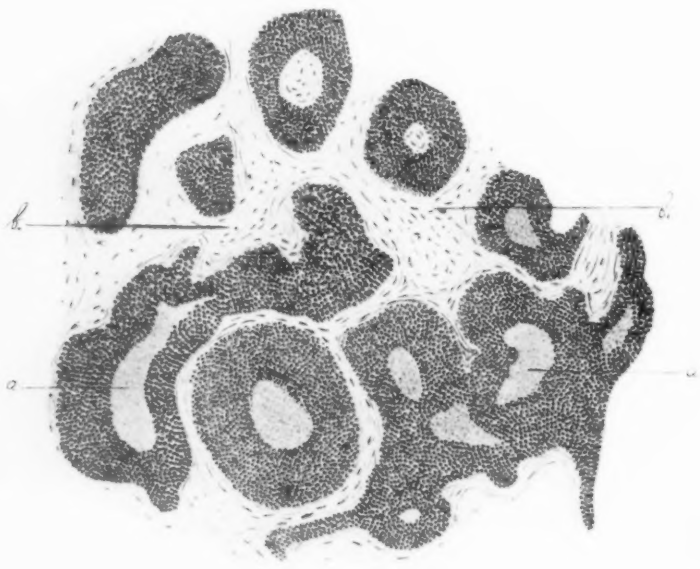

FIG. 5.—Intricate arrangement of stroma and epithelium in which it is difficult to interpret the appearances without the study of serial sections.

a.—Necrotic tissue.

b.—Stroma.

FIG. 7.—Showing the outward growth of intervillous epithelium and the flattening of the thereby produced diverticula against the muscular wall of the tube.

a.—Diverticulum filled with necrotic tissue.

b.—Beginning papillary proliferation of epithelium into the diverticulum (cyst).

c.—Muscular wall of tube—only a part of which is shown.

irregular nuclei which stain deeply throughout. Some nuclei also have long, twisted and irregularly tortuous extensions. Upon the ultimate border occurs a zone composed of dust-like granules of chromatin. In the necrotic tissue in which the free ends of the papillæ are embedded, there may be found occasionally cells distinguishable by their shape and size which have, however, lost all power to react to nuclear dyes; they assume the same tint with eosin as the granular material in which they lie. Leucocytes are present in the epithelial covering of the papillæ, but only as isolated cells; they are never accumulated in foci. Although often of the polymorphonuclear type, there are also many with small round nuclei. In the layers of epithelium they are easily distinguished from the epithelial cells in process of division, but in the outer bordering zones of necrosis they lose their identity. The leucocytes are often present in the walls of the vessels of the stroma.

The stroma or connective-tissue stalks upon which the epithelium is arranged to form papillary growths is very delicate (Fig. 4). It consists of but little more than a vessel wall. On each side of the lumen of the vessel are from three to six layers of parallel long cells which resemble the cells of involuntary muscle. Their nuclei are slender and from 20 to 30 mikrons in length and possess rounded or abrupt, blunt ends. The margins of these cells are obscure when in contact; but in advantageous places it is possible to see that the cells, like the nuclei, are spindle-shaped. Where papillæ have been cut across, the ends of the divided nuclei of these cells appear round and the nuclear membranes are much darker than when in longitudinal planes. Elastic fibers (Weigert's stain) are present neither in the walls of the blood-vessels of the connective-tissue stalks nor in the layers of cells which surround the vessels. The endothelial lining of the vessels is well preserved and shows no changes. There is some fibrin in some of the vessels and a small quantity in the necrotic tissue between the papillæ; in either case it never consists of more than a delicate network, extremely irregular. In sections from all parts of the tube examined it is possible to find villous outgrowths, the epithelium of which has become completely necrotic, but in which the stroma has not entirely lost its staining properties. Such papillæ, stained with Van Gieson's stain, show prolongations of the stroma extending for even long distances into the necrotic material before their nuclei, too, suffer chromatolysis. In some papillæ the epithelium is entirely necrotic upon both sides for only a short segment of its extent, the fuchsin-stained stroma bridging over the defect.

It is evident from the foregoing description that the papillary growths in this tumor consist mainly of an epithelial covering of many layers and that the proliferation of these has been so marked that they have filled the tube entirely, distended it to a marked degree and have undergone a considerable necrosis. The necrotic tissue has filled the enlarged channel. These growths have been referred to as stalks, as villous growths; when cut directly across, their outline is circular. Such circular bodies lying in the midst of the necrotic tissue have a striking appearance, since in certain sections they are found at considerable distances from any other tissue. Their outer margin is bordered by the dark circle of pycnotic nuclei and chromatin granules; the larger part of the body consists of the mass of epithelium with the radially disposed nuclei, and a small vessel containing numerous red blood-cells forms the center.

As might be expected, these villous growths have no regularity in their arrangement. The study of many sections cut in series shows that the entanglement is very intricate (Fig. 5). Arising from the wall of the tube, their course may be directly toward the lumen or oblique or even parallel to the wall. To complicate the arrangement, the villous growths frequently join one another as well as branch; consequently, in certain sections there may be seen at short distances from the muscular walls regions made up entirely of masses of epithelium, each mass consisting of a papilla cut obliquely or transversely, and containing in its center the blood-vessel. The edges of these clusters of epithelium may be in contact and the line of division difficult to find; in other places a narrow row of necrotic cells separates the epithelium of different papillæ; in yet other places the necrotic material has accumulated between them so that they appear well separated.

In deeper zones nearer the muscular walls still another peculiar appearance is obtained. Here the condition is reversed; the stroma borders the epithelium on the outside, and the epithelium lines a cavity filled with necrotic tissue (Fig. 6). The examination of serial sections shows that such cyst-like collections of cells are due to the growth outward, toward the muscular layers, of that part of the mucosa which intervenes between the villous prolongations; these outward growths, when cut across, appear like small cysts filled with necrotic tissue. As a rule the lining of these cavities at the inner margin is sharp and distinct. The layers of the epithelium are the same in character and number as those which cover the papillæ. It is essentially the same epithelium; the proliferation toward the lumen has resulted in villous growths; toward the muscular wall, in cavities; and these, when sectioned, appear like cysts. The necrotic material which fills them usually stains lightly and with eosin, but some are met with which are quite filled with chromatin granules; such cysts (so-called for convenience) have a darkly stained content. Naturally, such cavities are not always sectioned directly across; they often appear long and parallel to the muscular wall, or they are short and more oval. The muscular wall is bordered in this manner with but little interruption. It is obvious that the interpapillary proliferation outward toward the muscular wall has met with an obstruction; the distention of the tube has not been able to keep pace with the proliferation of the epithelium. Sections occasionally show the following condition: the inner border of the muscular wall of the tube is covered with the same epithelium in strata as has been described upon the papillæ. This epithelium lines a cavity the opposite wall of which is quite distant (the width of

the field, Obj. 3, Ocular 3, Leitz) and from the opposite wall small villous growths project toward the muscular wall; the remainder of the cavity is filled with necrotic tissue (Fig. 7). These cystic formations in some sections, with the tissue in which they lie, form a zone of considerable width just inside the muscular coats.

The tissue between the cysts is made up of the same elements as those described in the stroma of the villus, except that between the cysts it is abundant, whereas in the villi it is insignificant. It contains the long spindle cells, in all respects identical with those found in the villi; also many vessels in which are little more than loose-walled sinuses. Scattered leucocytes are seen frequently both with round and with irregular nuclei. The greater part of the stroma is apparently formed by fibers; some of them stain red with Van Gieson's stain; most do not. There are no elastic fibers among them. Numerous slender capillaries, which are so delicate that a single red corpuscle fills the lumen completely, are conspicuous in some sections in the stroma; with the iron-hæmatoxylin stain, by which the red blood-cells are made almost black, such capillaries, filled with blackened cells, form a distinct delicate network.

Very peculiar appearances are caused by the occurrence in the stroma, in certain places, of collections of blood-serum[64]—œdematous regions. The coagulated serum usually has small holes in it, oval in shape, which resemble the holes in the cells of a fatty liver; often leucocytes are found in the holes. The margins of the serum are beset with semicircular spaces; both the oval holes and the marginal defects are due to the shrinkage of the coagulated serum. In such œdematous situations, and in the tissue of the bordering zones, are found large swollen cells in all stages of dropsical degeneration; the wall of the cell forms a bag for the network produced by the vacuoles. Such vacuoles do not have the clear outline of holes which at one time contained fat. Often considerable fibrin occurs in the œdematous spots, and in places œdema is combined with hæmorrhage. Plasma or mast cells are not present in the œdematous districts or in the stroma elsewhere.

The question naturally presents itself: Are there any loose, unconnected, wandering epithelial cells in the stroma? A careful search for these was made in different ways. Many cysts were examined to see if at their outer margins there could be found any evidences of the proliferation of the epithelium outward into the stroma. Also many serial sections were examined to see if any of the collections of epithelium which form cysts were entirely unconnected and cut off; a third evidence of such a process was sought for, viz., cells in the stroma with nuclei in mitosis. All of these signs of invasion of the stroma by loose and wandering epithelial cells were absent. The proliferation of the epithelium has been *en masse;* by the proliferation of the tubal lining as a membrane; also by the production of a lining of many strata.

[64] The fluid of the blood is readily coagulated by hardening in solutions which contain chromic acid or its salts.

The muscular wall of the tube averages 1 to 2 mm. in width. The muscle fibers are few in number; sections stained by the picrofuchsin mixture reveal a large amount of fibrous connective tissue which takes a brilliant red color; this preponderance of fibrous tissue is especially marked in the inner half of the wall. The circular coat has undergone the greatest atrophy; only occasional strands of it are present.

The outer half of the fibro-muscular wall is more loosely arranged. There are many large, flattened blood-vessels in this portion and around them small aggregations of fat. In the inner one-half of the wall occur occasional clusters of lymphoid cells that show the effects of pressure, being greatly elongated and parallel with the fibers. Such lymphoid nodes made up entirely of cells that correspond to small lymphocytes occur in all sections. In a few sections there are islands of cells that present a different appearance; closely aggregated cells with pale nuclei form an elliptical clump that possesses a very definite margin. Careful examination fails to reveal any nuclear figures in these cells; their nuclei possess very little chromatin; their arrangement is quite irregular; for these reasons and the fact that no lining cells can be found for the spaces in which they lie, a conclusion was reached that these islands have resulted from the proliferation of the endothelial lining of lymph channels. Still other islands of cells leave no doubt but that the proliferating epithelium has penetrated deeply within the fibro-muscular wall. In a few sections, lying nearer the inner border of this wall, are irregular tubules lined with epithelial cells. The nuclei of the cells are long, occupy most of the cell and stain deeply. The cells are columnar and in places two or three strata in depth. Some of these tubules occur within lymph channels, for outside the deeper and more columnar cells the endothelial lining of the channel is easily recognizable. Since these deeper prolongations of the epithelium were found so seldom, no effort was made to prove their connection by serial sections with the more centrally located parts of the tumor. The ovary contained no tumor tissue.

From Dr. W. W. Sheppard, the family physician, it was learned that for some time after the operation the patient was "nervous and hysterical," but improvement was steady and she was soon able to be up and around the house a part of each day. About nine or ten weeks after the operation ascites reappeared and upon vaginal examination a tumor, the size of an orange, was found on the left side. The ascites was relieved by tapping two or three times, the first being done on November 1st. During the month of December Dr. Byron Robinson was called in consultation. He has informed me that he found the abdomen enormously distended by a large tumor and considerable ascitic fluid. The patient was sitting up and able to walk about the house; her general appearance was cachectic, pulse 120, temperature 100° F. The tumor arose from the small pelvis and upon vaginal examination was found to be fixed, except its uppermost portion, which was slightly movable. It was

located chiefly on the left side. The uterus was slightly enlarged.

Operation (by Dr. Robinson).—Upon opening the abdominal cavity with a long median incision the entire peritoneum was found studded with papillomatous growths which varied in size from those barely visible to some as large as a hen's egg. The larger ones were located in the lower, left quadrant of the cavity, and in this position were adherent to one another so as to form an irregular mass. There were approximately two gallons of a clear ascitic fluid, similar in tint to pale ale, in the cavity. The irregular tumor on the left side was firmly adherent to the left lateral wall of the small pelvis; it extended upward so as to be in front of the sigmoid; the omentum was firmly adherent to it, and in the omentum near the tumor and also in the adjacent mesentery were many small shot-sized and pea-sized warty growths. Most of these growths had a pale yellowish color and were like a fresh brain in consistency; some of the smaller growths appeared very vascular. All of the larger growths were removed.

Recovery followed the second operation without any special events. At present she is able to perform some of her customary household duties. The ascites returned gradually so that about five months after the second operation paracentesis was necessary for the patient's comfort; and it has been practiced every two or three weeks since. At one time eleven quarts were removed, at another twelve quarts; the fluid maintains its former characteristics. A sample of this fluid showed on examination the following features: sp. gr. 1007, alkaline reaction, a large amount of albumin, absence of sugar, a moderate amount of proteids (biuret reaction), absence of bile, and .3 of 1 per cent of urea. I received the tumor masses removed by Dr. Robinson after they had been in a weak aqueous solution (4 per cent) of formalin for several days.

Macroscopic.—They consist of three large masses and about a dozen smaller; altogether they weigh 1,350 grammes. The largest piece measures $16 \times 13.5 \times 4$ cm. and is disk-shaped; on section it presents a granular surface which resembles somewhat adipose tissue. Its external surface is smooth except for tag-like, torn adhesions. Its concave side has a furrowed and trabeculated appearance. The next smaller in size is very irregular in form, measuring $12 \times 10 \times 5$ cm.; it is very rough and nodular externally and in spots has been torn. The smallest of the large pieces measures $11 \times 7.5 \times 4.5$ cm., and on section is found to possess a much softened, necrotic center. One of its flat surfaces is quite smooth. All of the smaller masses are very irregular; some appear to be little more than fibrous tissue, others resemble the larger masses.

Microscopic (continued).—Sections were made of all the large growths, and some of the smaller, and stained by various methods. A large part of all the growths consists of necrotic tissue; many sections contain little else. The necrosis is most marked in and around the central portions; such necrotic tissue stains lightly or darkly according to the degree of chromatolysis; varying degrees of œdema and quantities of fibrin occur as well as small hæmorrhages. In sections where necrosis is less marked, the appearance of the innermost parts of the tubal tumor are duplicated; here occur cross-sections of papillæ lying in the necrotic tissue which are in all respects similar to those in the tube in size, shape, paucity of stroma and number of epithelial strata; the epithelial cells contain similar large nucleoli. Karyokinetic figures, however, are much more numerous; often three, four or six dividing nuclei are present in a single field of the immersion objective (celloidin sections, 15 to 20 mikrons thick). The stroma of the papillæ—connective-tissue stalks—has its origin in a capsule which surrounds each metastatic growth more or less completely. The capsule is formed by long cells arranged parallel to the circumference whose oblong nuclei contain nucleoli which are barely visible; these cells are not arranged in layers, for the nuclei have been cut in all possible diameters; the cells resemble the "fibroblasts" of organizing granulation tissue. In sections of the various metastatic growths, and even in different sections of the same growth, the capsule shows large blood-vessels, regions of necrosis and of hæmorrhage and thrombosed vessels. In regions just internal to the capsule, where the papillomatous growths have been so luxuriant that the papillæ are in contact and a tissue has been produced which appears solid and granular, if the stroma be examined in such places *the connective-tissue cells are also found with mitotic figures.* They are never as abundant as the dividing nuclei of the epithelium; that the stroma or supporting tissue contains cells which are multiplying is beyond doubt; that these cells are the same as those which constitute the stroma is also certain, since all stages of multiplication by indirect division may be found and also for the reason that there are no other cells in the stroma with resting nuclei than those described. It may be inferred that this difference between the stroma of the papillæ in the primary tumor and that in the papillæ of the metastatic growths is due to more favorable conditions of nutrition; it is also possible that the more rapid proliferation of the epithelium, as is shown by the abundance of dividing nuclei, has in itself led to a proliferation of the cells of the framework, and that this has been sufficient in amount to allow the observation of occasional dividing nuclei in the stroma cells.

This condition of embryonal stroma and embryonal epithelium, since both contain dividing nuclei, has resulted in a line of demarcation where epithelium and connective tissue meet, which is much less distinct than similar lines of contact in the primary tumor. In regions close to the capsule, where there has been a rich growth of papillæ and necrosis has not occurred, the indistinct line of contact and the entanglement of papillæ renders it difficult to distinguish between epithelium and connective tissue. Some aid may be had from the columnar position of the nuclei of the epithelium on the stroma, but this does not always obtain; in other places the epithelium has contracted away from

the stroma so that a narrow space is present. The blood-vessels in the stroma have very little wall; they resemble the vessels commonly encountered in a small spindle-celled sarcoma.

Among the tumors of the Fallopian tube that can be considered as carcinomata, this case is unique in the following particulars: The os abdominale was evidently open, since there was not formed the usual sac, and invasion of the peritoneal surface and adjacent tissues probably took place via this opening by continuity of surface. The case is also remarkable in that large secondary tumor masses were removed from the abdominal cavity, the patient still living, although slowly succumbing to the disease.[65] The similarity in method of growth and general histologic structure to proliferating cystadenomata of the ovary is continued in the comparative benignancy of the peritoneal metastases.

The appended table comprises 21 cases of carcinoma that were selected from 52 cases that have been reported as papilloma or carcinoma. 15 of the 52 were excluded by reason of insufficient data; of the remaining 37 some have been shown to be instances of hyperplasia of the tubal mucosa due to inflammation, a process usually combined with sacto-salpinx, that leads to the formation of benign localized growths whose position in the domain of tumors is very questionable, or to more diffuse growths that may possess some of the characteristics of malignancy; the latter resemble the carcinomata that develop in scars, burns or fistulæ from long-continued irritation.

[65] The patient died February 18, 1901; through the kindness of Dr. Sheppard, a necropsy was secured, the details of which will be shortly published.

AUTHOR, TITLE AND PLACE OF PUBLICATION.	BILATERAL OR UNILATERAL.	CONDITION OF THE OPPOSITE TUBE.	CLOSURE OF OS ABDOMINALE AND FORMATION OF A SAC.	RECURRENCE OR RECOVERY. DEATH SOON AFTER OPERATION.	CONCERNING METASTASIS, INVASION OF ABSCESS CAVITIES, ETC.	CONDITION OF THE OVARIES.	REMARKS.
E. Senger: Ueber ein primäres Sarkom der Tuben. Centralbl. f. Gynäk., 1886, X, p. 601, Leipzig.	Bilateral.		In both tubes there occurred two dilatations or sacs.	Tumor found at necropsy.	In Douglas's pouch a small growth.	Both normal.	Reported as sarcoma.
E. G. Orthmann: Ueber Carcinoma Tubæ. Ztsch. f. Geburtsh. u. Gynäk., 1-88, XV, p. 212, Stuttg.	Right tube.	Pyosalpinx.	The outer end, greatly dilated opened into an abscess cavity.	Death on sixth day after operation.	The tumor had invaded two abscess cavities. A small nodule in the "excavatio vesico-uterina." A swollen lymph gland in the small pelvis.	Abscesses in both ovaries.	
A. Doran: Primary Cancer of the Fallopian Tube. Tr. Path. Soc. (London), 1888, XXXIX, p. 208.	Right tube.	Left tube at operation appeared small.	Outer end closed: a sac formed.	Recurrence; lived nearly eleven months after operation.	Lumbar glands invaded.	R.—cancerous.	At necropsy, tumor found in the uterine vesical and vaginal mucosa.
C. J. Eberth and R. Kaltenbach: Zur Pathologie der Tuben. Ztsch. f. Geburtsh. u. Gynäk., 1889, XVI, p. 357, Stuttg.	Bilateral.		L.—dilated to size of thumb. R.—larger (faustgrösse.)	Recurred in 18 months.	Subperitoneal nodules noted on the right tube.		Demonstrated first as carcinoma. Reported later as papilloma.
T. Landau and J. Rheinstein: Beiträge zur pathologischen Anatomie der Tube. Archiv f. Gynäk., 1890-91, XXXIX, p. 273, Berl.	Right tube.	Outer end closed and a sac formed that contained 500 ccm. of bloody, thin fluid.	Sac formed on right side.	Recurred in 10 months.	Ascites after the operation, with hard masses in the abdomen.	Normal.	
S. D. Michnoff: A Case of Primary Carcinoma of the Fallopian Tubes (Russian). Meditsina, 1891, III, p. 181, St. Petersb.	Left tube.	Sacto-salpinx papillomatosa.	Left tube formed a sac as large as a large fist.	Recurrence in 7 months.	A cyst occurred at junction of right tube and ovary, size of a hen's egg; it was filled with clear fluid.	L.—ovary left in body, it was imbedded in adhesions. R.—normal.	
P. Zweifel: Vorlesungen über klinische Gynäk., 1892, p. 139, Berlin.	Bilateral.		Large sacs on both sides. L. tube 20 cm. long and 8 cm. thick.	Presumably recurrence, since patient died 1½ years after operation.		Normal.	
F. J. E. Westermark and U. Quesnel: Ett fall af dubbelsidig kancer i tubæ Fallopii. Nord. Med. Ark., 1892, XXIV, Nr. 2, p. 1, Stockholm.	Bilateral.		Sacs formed on both sides—larger on left.	Recurrence: death in five months.	Invasion of cyst of right ovary. No exudate in peritoneal cavity at necropsy. Lymph glands of small pelvis invaded. T.—nodules found in the liver at the necropsy.	L.—ovary cystic. Monolocular cyst size of an orange.	Carcinoma of the cervix found at the necropsy.

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R. Kretz: Zur Casuistic der Papillome der Eileiter. Wien. klin. Wchnsch., 1894, VII, p. 572.	Bilateral.		L.—tube 17 cm. long and 6 to 8 cm. in diameter. R.—tube similar. Both closed externally.		Small subperitoneal nodules noted, externally on both tubes. Invasion of the lymph channels, (histologic examination).	Unknown.	Reported as papillomata. Kretz considers the case similar to that of Eberth and Kaltenbach.
W. Fischel: Ueber einen Fall von primärem papillärem Krebs der Muttertrompeten. Laparotomie, Heilung. Ztsch. f. Heilk., 1895, XVI, p. 143.	Bilateral (?)	Condition of left tube not positively known. It was imbedded in adhesions and not removed.	R.—tube formed a sac 8 by 4.5 cm.	Recurrence: death seven months after the operation.	Small nodules on external surface of right tube. Abdominal cavity contained clear ascitic fluid.	Unknown.	Part of the cyst of the right tube possessed a smooth wall covered by a single layer of short epithelium.
A. Rosthorn: Primäres medulläres Carcinoma tubae. Ztsch. f. Heilk., 1896, XVII, p. 177.	Right tube.	At necropsy left tube found to contain metastatic (?) tumor nodules.	Sac formed by right tube supposed to be pyosalpinx.	Recurrence: death six months after first operation.	Inguinal glands removed at a second operation. Retroperitoneal glands found invaded at the necropsy.	Cyst of right ovary.	Necropsy by Chiari.
T. J. Watkins (and E. Ries): Exhibition of unique microscopic sections of papilloma and carcinoma of the tubes, etc. Am. Gyn. and Obst. J., 1897, XI, p. 272, N. Y.	Bilateral.		Both tubes large and formed by four convolutions; both closed externally.	Recurrence: death seven months later.	Ext. end of the right tube connected to a mass 4 × 4 × 5 cm. This contains a central cavity beset with several warty growths. Metastatic carcinomata on the ovaries and on post. surface of right tube. Collections of tumor cells found in lymph channels of wall of left tube.	L.—ovary many corpora candicantia.	Condition of right ovary not clear.
E. Falk: Fortschritte u. gegenwärtiger Stand der vaginalen Operations technik. Therap. Monatsh., 1897, XI, p. 313, Berl.	Left tube.	Unknown.	Left tube closed externally. Sac formed.	Recurrence: death seven months after operation.		L.—ovary normal.	Tumor found in the uterus in mucosa near right ostium and diagnosed as sarcoma was supposed to be responsible for recurrence and death.
K. Eckardt: Ein Fall von primärem Tubencarcinom. Arch. f. Gynäk., 1897, LIII, p. 181.	Left tube.	Normal. (Doran).	Sac formed by the left tube size of child's head.	Healthy a few months later. Subsequent history unknown.	Subperitoneal elevations, size of nazel-nut, make external surface irregular.	Both normal.	Broad ligament shortened by invasion of the tumor.
A. H. Pilliet: Épithélioma de la trompe utérine. Bull. Soc. Anat. de Par., 1897, XI, p. 956.	Right tube.	Unknown.	Cavity in the right tube opposite ovary.	History not known.	Invasion of the lymph channels, (histologic examination.)	Condition of left ovary unknown. R.—invaded by tumor in its outer part only.	
C. H. Roberts: A Case of Primary Carcinoma of the Fallopian tube. Tr. Obst. Soc. London, 1898, XL, p. 189.	Right tube.	"The left tube inflamed and closed."	Outer end of right tube closed: sac formed.	Well ten months later.		Normal.	Very brief histologic description.
J. Fabricius: Beiträge zur Casuistik der Tubencarcinome. Wien. klin. Wchnsch. 1899, XII, p. 1230.	Left tube.	At first operation the right adnexa appeared normal; at second, thickened.	Supposed to be a pyosalpinx until it was cut.	Recurrence five months later when a large mass filled the right half of the pelvis.		Unknown.	At the first operation masses removed were pronounced papilloma. At the second operation when radical removal was found to be impossible, masses were removed that were pronounced carcinoma.

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J. Fabricius: Idem.	Right tube.	L.—adnexa appeared normal at the operation.	Abdominal opening leads into a cyst.	Recurrence: five months after first operation left adnexa and uterus were removed.	Carcinomatous invasion of the cyst on right side. At the second operation it was found that the entire peritoneum was beset with small tumor nodules. The metastatic nodules on the outer surface of the uterus were examined and pronounced adenocarcinoma.	Right ovary enlarged but otherwise normal.	After second operation a large cyst developed that reached upward to the navel and finally evacuated through the rectum.
Danel: Essai sur les Tumeurs malignes primitives de la Trompe Utérine, 1899, Paris.	Left tube.	Appeared healthy at operation. Not removed.	Left tube formed a sac.	Recurrence took place on the right side.	Many peritoneal growths on the uterine end of the tube. Enlarged glands in the adhesions around left tube. Tumor cells found in the lymph channels. (Histologic examination.)		
B. Friedenheim: Beitrag zur Lehre vom Tubencarcinom. Ueber ein primäres, rein alveoläres Carcinom der Tubenwand. Berl. klin. Wchnsch., 1899, XXXVI, p. 542.	Left tube.	Unknown.	No sac formed.	History subsequent to operation unknown.	Left tube and tumor adherent to colon. Left parametrium infiltrated with tumor masses.	L.—smooth externally, size of a walnut, contained small cysts.	Tumor said to have had its origin in an accessory tube.
E. Mercelis: Primary carcinoma of the Fallopian tube. N. Y. Med. J., 1900, LXXII, p. 45.	Right tube.	Left tube removed. Condition not described.	Right tube 4 cm. in greatest diameter. Outer end closed.	Recurrence on right side 18 months later.	Outer end of right ovary invaded by tumor.	L.—ovary small and firm—not removed. R., the seat of chronic interstitial changes.	

REPORT UPON A CASE OF GONORRHŒAL ENDOCARDITIS IN A PATIENT DYING IN THE PUERPERIUM; WITH REFERENCE TO TWO RECENT SUSPECTED CASES.

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AND

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Case 1.—I. T., aged 19, unmarried, was admitted to the Obstetrical Department of the Johns Hopkins Hospital on February 13, 1900, complaining of fever and weakness which she thought were of puerperal origin.

Family History.—Negative as far as could be ascertained.

Personal History.—There is no history of the ordinary diseases of childhood, nor of any acute infectious disease. She has never had rheumatism, and states that previous to the onset of the present illness she has always been a healthy woman.

Marital and Menstrual History.—The patient is unmarried, and has had no previous children or miscarriages. The menstrual history is normal in all respects.

Present Illness.—The patient states that she was confined on January 19, 1900, after a hard but non-instrumental labor at term. (Child living.) During the course of the labor frequent vaginal examinations without aseptic or antiseptic precautions were made by those in attendance, and the third stage of labor was furthermore complicated by a retained placenta, which, after several attempts was removed manually, likewise without precautions. On the fourth day of the puerperium she was seized with a chill, followed by fever, and, later, sweating, and these symptoms have recurred regularly every day since then. Other symptoms have been headache and general pain in the limbs, nausea and vomiting, the latter at times marked, and almost complete loss of appetite. For the past few days she has had, in addition, a rather constant cough, accompanied by some pain in the

side. The patient says she has been confined to bed practically ever since labor, and, though she has felt at times better than at first, she has grown progressively weaker.

Physical Examination.—The patient's mental condition is very dull apparently, answering questions poorly, and only when repeated and asked in a loud voice. Well-formed and well-nourished woman, marked anæmia present, the lips and mucous membranes being almost bloodless. Temperature on admission 102.4° F., pulse 120.

Thorax.—Well formed. Respirations rather hurried, with an occasional short, sharp cough.

Lungs.—Expansion fair, equal on the two sides. Vocal fremitus normal. Percussion note normal throughout. On auscultation at the base of each lung, a few very fine crackles are heard on deep inspiration, and here and there over both lungs an occasional medium moist râle. The breath-sounds are normal.

Heart.—The point of maximum impulse is neither visible nor palpable. No thrill or shock on palpation. Apparently no increase in the area of cardiac dulness. On auscultation at the apex both sounds are practically obliterated by a to and fro murmur, the systolic being the louder and more intense. Both murmurs are transmitted and well heard in the axilla. Preceding the systolic murmur a rather loud rumble is heard at the apex, which is likewise transmitted to the axilla. Over the body of the heart both murmurs are well heard. Over the base the systolic murmur becomes diminished in intensity, the diastolic more clear-cut and marked. The presystolic rumble is lost. The pulse is markedly collapsing in character, and there is a distinct capillary pulse present.

Abdomen.—Looks normal. No rose-spots are visible. There is no distension and the abdomen is everywhere soft on palpation.

Spleen.—Not palpable.

Liver.—No apparent increase in dulness. The edge is just palpable at the costal margin.

On palpation no mass can be felt in the pelvis on either side or in either iliac fossa.

Legs.—Œdematous and slightly swollen. No swelling or other changes in the joints noted.

Following admission on the morning of February 13th, the patient had several vomiting spells, attended by signs and symptoms of collapse, her skin becoming cold and clammy, and her pulse dropping from 120 to 80-90 to the minute, with an occasional intermission. When first seen in the afternoon, several hours after admission, the patient looked septic, but seemed to be in fair general condition. Temperature at this time was 101.6° F., pulse 112 to the minute, rather weak and of poor volume and tension. When seen again about 7.30 P. M., she was found to be in far better general condition, though markedly drowsy. Her history was taken at this time, and the physical examination made. A provisional diagnosis of ulcerative endocarditis of the aortic valve, secondary to puerperal infection, of probably streptococcic origin, was made at this time. During the night the temperature again rose, reaching its maximum, 103° F., about midnight, pulse 120 to the minute and much weaker. The general condition became very much worse, there being marked prostration with drenching sweats as a particularly noticeable feature. About 8.30 A. M., February 13th, the temperature had fallen to 100.8° F., the pulse, 80 to 90 to the minute, and of poor volume and tension. Attacks of vomiting, attended by increasing signs of collapse, continued, and the general condition seemed very much worse than at a corresponding time last night. Material for taking a culture from the uterus was secured about 9 A. M., a fair amount of bloody lochia being obtained.

The perineum was found practically intact. On vaginal examination the uterus was found enlarged, apparently normally involuted, according to the history, and slightly retroposed. The cervix was slightly torn. The adnexa seemed normal.

About an hour and a half later, the condition remaining about the same in the meanwhile, the patient had another very severe attack of vomiting, with great collapse and much sweating, so that, in spite of stimulation and subcutaneous infusion of normal salt solution, the pulse, which had fallen to 60 to the minute and was very weak and intermittent, gradually became weaker and finally ceased at the wrist, the patient dying shortly thereafter.

Blood.—An examination of a fresh blood specimen was made about 9.30 A. M., February 13th, and found negative for malarial organisms. Apparently a leucocytosis was present.

Urine.—Examination of a specimen obtained during the night showed a distinct whitish flocculent precipitate, a distinct trace of albumin, no sugar, and no diazo-reaction. Microscopically a number of hyaline and some epithelial and pus casts, a number of pus cells and some epithelial cells, and a number of micro-organisms, some of which showed motility, were found.

Uterine Culture.—Cover-glass specimens, stained with gentian-violet, showed a few epithelial and some pus-cells, and possibly an occasional coccus or in doubtful pairs, but so few in number that it was impossible to say whether they decolorized by Gram's method or not. Cultures taken on bouillon, agar plates (2 dilutions), and anaërobic glucose agar, all remained sterile.

The history pointing so clearly to puerperal infection, the possibility of the gonorrhœal nature of the trouble was not thought of, and, in consequence, no attempt was made to obtain the gonococcus culturally from the uterus.

Pathological Report.

Autopsy No. 1487, February 14th, 7.45 P. M., by Dr. W. G. MacCallum.

Anatomical Diagnosis.—Acute vegetative and ulcerative endocarditis, involving aortic, tricuspid and pulmonary artery valves. Acute splenic tumor. Infarction of spleen. Catarrhal cystitis. Puerperal uterus.

The body is that of a young, well-nourished woman, whose breasts are in the puerperal state.

Upon section, the peritoneal cavity is found to contain very little fluid, and the serous membrane is smooth and glistening.

The pelvic cavity contains a small amount of a brownish, slightly turbid fluid.

The omentum is bound down between the liver and spleen by fresh adhesions over a small area.

The pericardium, upon being opened, contains a small amount of feebly turbid fluid, but its serous surfaces are smooth and glossy.

The Heart.—Weight 325 grams. The epicardium is smooth. The right auricle is normal. The foramen ovale is open to the extent of 3 mm. The ductus Botalli persists as a cord.

The tricuspid valve is delicate. Upon the posterior leaf, abutting upon the septum ventriculorum, is a large lobulated vegetation which begins at the base of the valve and extends to its edge, hanging into the intervalvular space on the auricular surface of the valve. A granular mass also exists behind the valve, between it and the septum and lying upon the latter. The leaflet lying to the left of this as the heart is opened, shows a few minute pin-point translucent elevations on its auricular surface. The larger lobulated vegetations are opaque and yellowish and surmounted by soft post-mortem clots.

The pulmonary artery valves are delicate. At the junction of the right and left leaflets are small translucent vegetations on the ventricular surface.

The left auricle is normal.

The mitral valve is normal.

The aortic valves are most extensively involved, the posterior segment alone being free from vegetations. The left segment is surmounted on the ventricular side by a large mass of lobulated vegetations which extend down on to the ventricular wall. There is considerable roughening of the endocardium of the ventricle below the right segment also. The inner surfaces of these two segments in the sinuses of Valsalva are roughened and covered by soft dark-colored post-mortem clots. From the right sinus of Valsalva a probe can be passed through an opening in the septum ventriculorum into the vegetations on the ventricular side in the right ventricle behind the tricuspid valve. This opening has probably been caused by an extension of the inflammation through the septum.

The heart muscle is rather soft and brown in color.

Measurements: Circumference of tricuspid valve, 12 cm.; right ventricle, 8.5 × 4 cm.; circumference of mitral valve, 8 cm.; left ventricle, 7.5 × 12 cm.; circumference of aortic valve, 7.5 cm.

The lungs present a moderate degree of œdema; otherwise they appear normal.

Spleen. Weight 300 grams. Measures 18 × 8 × 6 cm.

Excepting over two areas, one on the anterior surface where the organ touches the liver, and the other at the posterior edge, the spleen is quite smooth. Corresponding to those areas of roughness the spleen is indurated and elevated. The anterior area is adherent to the liver by fresh adhesions, whilst over the posterior area are found a few fibrous adhesions only.

On section, these elevated firm areas are found to present the features of typical anæmic infarcts and are wedge-shaped. The spleen is soft and light purple in color. The great increase in bulk being in white spleen pulp. The Malpighian bodies are greatly enlarged and prominent, with irregular margins, measuring 3 mm. in diameter. The splenic pulp proper is not very greatly increased, but seems very soft and succulent.

The Liver.—Weight 1600 grams. Surfaces are quite smooth excepting where the organ is adherent to the spleen.

Gall-bladder and ducts are normal.

On section, it is soft and flabby and greasy to the touch. The lobules are quite definitely marked out; the centers being translucent, beyond them comes a congested zone, then outside of it is a zone of pallor and yellow opacity.

The Kidneys.—Each weighs 175 grams, and in all respects are alike apparently. They are slightly larger than normal, and the capsules strip off readily. The stellate veins are markedly injected, and between them the parenchyma has a grayish look.

On section, the cortex is thickened and measures from 5-8 mm. The striations are fairly well marked. The glomeruli are visible, but there is, however, some opacity and an appearance of being much swollen in the labyrinthine portion. The lines and dots of yellow opaque material are quite noticeable. The pelves contain a thick yellowish fluid, but they are not, however, especially injected.

The ureters are apparently normal.

The *urinary bladder* contains a small quantity of thick, yellowish puriform fluid, and the mucosa is in places deeply injected.

The *uterus* is enlarged and soft. The mucosa is somewhat congested, but there is no sign of inflammation (measurements of organ not given).

Fallopian tubes and ovaries are normal.

Lymphatic glands are nowhere especially enlarged.

The bone-marrow (femur) is somewhat reddened.

Other organs and tissues appear normal.

Microscopical Examination of Tissues.

Heart muscle shows œdema and fragmentation (?).

Lungs also show general œdema, leucocytosis in blood of all vessels, and some local atelectasis.

Mammary glands show evidences of being in the normal state of lactation.

Spleen shows a state of general enlargement. The portion containing the infarction could not be found, having been inadvertently mislaid.

Liver presents evidences of chronic passive congestion with fatty metamorphosis.

Kidneys. A moderate degree of parenchymatous nephritis is noted, accompanied by a few foci of small round cells, which also occur in the walls of the larger arteries.

Intestines exhibit simply post-mortem degeneration, and evidences of leucocytosis in their blood-vessels.

Fallopian Tubes. Mucosa normal; blood-vessels give evidence of a leucocytosis.

Uterus. Sections were cut from three sites:—

(*a*) Cervix (including part of vaginal portion).

(*b*) Body (1, about the middle; 2, at the fundus).

These were stained in hæmatoxylin and eosin, methylene blue, by Weigert's and by Gram's methods.

(*a*) *Cervix*, on being stained in hæmatoxylin and eosin, presented the following features: The vaginal portion gave evidence of post-mortem degeneration only; likewise in the lower part of the canal similar changes are found, and dense masses of material staining blue in the hæmatoxylin can be made out readily in small clefts in the disintegrated tissue, being in all probability bacteria.

The mucosa of the upper portion of the canal shows no evidence of post-mortem change; it appears quite ragged and adhering to it in places are masses of what seem to be broken down red blood-corpuscles.

The submucosa is much richer in small round cells than is normal, and scattered about in moderate numbers are phagocytic cells containing altered blood pigment. In places where evidences of mucous glands exist, it is found that they are choked with shed epithelium, at times retaining its columnar form and at others being changed into granular detritus staining well in eosin and showing much nuclear débris.

Throughout the remainder of the section is noted a more or less well developed degree of œdema, best marked towards the parts beneath the mucosa. This œdematous fluid contains large numbers of small round cells, a few plasma cells, and moderate numbers of large mono- and polymorphonuclear cells which frequently are seen loaded with altered blood pigment, few in number and located deeply in the lower portion of the section, but higher up much more numerous and approach the mucosa, where they may be found lying in close contact to the deposits of broken down red blood-corpuscles.

The blood-vessels everywhere are greatly dilated and show evidence of marked leucocytosis, in which the polymorphonuclear cell prevails, but both large and small mononuclear cells are by no means scarce.

The arteries show no signs of either peri- or endarteritis, but in some instances their walls are thickened, due to hypertrophy of the muscular coat. Amongst the larger arteries can be seen at times small, irregular areas of a hyaline nature which stain brightly with eosin. The vasa vasorum give no evidence of inflammation.

The veins, especially along the course of the smaller ones, show at their peripheries considerable small, round-cell accompaniment.

Stained with methylene blue, the section presents no definite signs of the existence of micro-organisms. Notable, however, is the presence of numerous mast-zellen, more numerous in the deeper portions of the section than in the superficial parts.

Gram's stain, with Bismarck brown as counter-stain, simply brings out the presence of mast-zellen even more sharply than with methylene blue, but presents no signs of bacteria.

Weigert's stain shows no bacteria to be present.

(*b*) *Body of Uterus.*—Stained in hæmatoxylin and eosin.

Mucosa much thinner than normal. No columnar epithelium found. No placental tissue was noted. A few mucous glands could be identified and were found filled with shed columnar epithelium, mucus and some small round cells.

The general condition is similar to that described under cervix section, but, if anything, the small round cell infiltration is more intense, especially between the muscle-bundles.

The arteries show the same hyaline masses and there is no inflammation of the vasa vasorum. Occasionally seen in section from fundus, but more noticeably in the section from the middle portion of uterus, is a great thickening of the adventitious coat of the larger arteries and so dense that in places it resembles old dense hyalinized fibrous tissue. In these arteries the lumina can scarcely be traced and, in fact, a few show no lumina whatever, and their general course is a very tortuous one.

Sections stained in methylene blue, Gram's or Weigert's stains, show no evidence of bacteria, but as before in cervical sections, show presence of mast-zellen whose granules at first glance might be mistaken for cocci.

Coverslip preparations were made from

(*a*) the valvular vegetations,

(*b*) the pericardial fluid,

(*c*) the splenic infarct,

(*d*) the pelvis of left kidney,

(*e*) the contents of the urinary bladder.

Negative findings were recorded for (*e*), (*c*) and (*d*). Slips from the vegetations showed the presence of large numbers of cocci, occurring singly, in pairs, in fours and in clusters; also, in numerous proportion, the various kinds of leucocytes, the polymorphonuclear type greatly preponderating. The cocci for the most part appeared lying free, but not infrequently they occurred within cells. Typical biscuit-shaped organisms were by no means the rule. They readily decolorized by Gram's method of staining.

The preparations from the urinary bladder exhibited several varieties of bacilli and cocci, but of the latter none could be said to resemble the gonococcus.

Cultures.—Unavoidable necessity delayed the use of special media for fifteen hours, but cultures in plain agar were made at once from

(*a* and *b*) Aortic and tricuspid vegetations.

(*c*) Splenic infarct.

(*d*) Heart's blood.

(*e*) Left kidney.

(*f*) Urinary bladder.

These cultures were poured into Petri dishes and incubated at 36.5° C. for 48 hours and then examined.

Results on plain agar:

(*a*) Aortic vegetations yielded the gonococcus, Streptococcus pyogenes, Bacillus coli communis.

The isolation of the gonococcus on the plain agar was due to its having developed in a small fragment of blood-clot which had been carried over in making the culture. It was positively identified as such by its inability to grow on plain agar or ox-blood serum, but growing luxuriantly upon hydrocele fluid agar, and finally by decolorizing in Gram's stain.

(*b*) Tricuspid vegetation gave the above organisms with the exception of the gonococcus.

(*c*) Splenic infarct remained sterile.

(*d*) Heart's blood gave bacillus.

(*e*) Kidney was grossly contaminated by bac. subtilis.

(*f*) Urinary bladder yielded the Streptococcus pyogenes, Bacillus coli communis.

Cultures in hydrocele fluid agar were made from

(*a*) and (*b*) Vegetations on aortic and tricuspid valves.

(*c*) Splenic infarct.

These were incubated for 48 hours at 36.5° C. and then examined.

Three types of colonies were found, resembling those of B. coli communis, Streptococcus pyogenes and gonococcus. Transfers were made at once of the two former organisms to plain agar-slants, and of the latter to hydrocele fluid agar and plain agar-slants. Typical growths of the colon-like bacillus and of the streptococcus were obtained on the plain agar, and upon the hydrocele fluid agar isolated colonies identical with those of gonococcus grew out. Strange to relate, of fifteen plain agar-slants inoculated as checks from the suspected gonococcus colonies, two showed slight but definite growth of a scarcely perceptible nature, which, upon examination, yielded a diplococcus identical in morphology and tinctorial reaction with the gonococcus. These two growths were transferred again to plain agar and also to hydrocele fluid agar with the result that upon the latter medium only did development occur, and further attempts failed to produce growth from these hydrocele fluid cultures upon plain agar.

This same result Dr. Young states has at rare intervals come under his notice also in the work of the genito-urinary clinic.

That the third type of organism isolated from these plates was the gonococcus is proven by its failure to grow upon plain agar (excepting the two instances noted beforehand) and upon ox-blood serum and other ordinary media, by its being able to grow upon media containing human blood (as noted on the plain agar plate) or human serum when grown at 37° C., and by its inability to retain the stain when treated by Gram's method.

Case 2.—Medical No. 9274. W. A., æt. 28.

Was admitted to Ward F on November 25, 1898, being sent in as a supposed case of typhoid fever. Patient complained of pains in the stomach, heart and kidneys.

Family history was of no importance.

Past History.—As a child he had measles and possibly typhoid fever. At 22 years of age he had an indefinite illness which was treated as smallpox, typhoid fever and diphtheria, during the course of which there occurred a swelling below the right ear which, on being opened, discharged pus. There is an indefinite history of malaria following three weeks after the above illness, which was cured by quinine.

Patient never had any urinary disturbances nor pains in lumbar region. He had gonorrhœa three years ago, accompanied by an inguinal bubo which did not suppurate; there were no other sequelæ.

The patient denied syphilis; he was a moderate drinker.

Present illness began on September 26th. He partially recovered, but soon got worse again. He first noticed a general weakness, and had "dumb chills" for three weeks daily, followed by moderate sweats; there was neither nausea, nor vomiting, nor herpes, nor diarrhœa. He then got steadily worse and was confined to bed for 4-5 weeks. Improvement followed so that he got out of bed and staid in his room one week, then went about the house, but four days later he had a relapse, which, the patient thinks, turned into typhoid fever. This happened about a month ago; since then he was in bed until two weeks ago, when he got up and walked around, but owing to swelling of his legs and consequent stiffness, he returned to bed. In this period he had herpes and night-sweats, although during the last three weeks the latter have been absent; likewise he experienced for the first time palpitation of the heart and shortness of breath, accompanied by a rather bad cough, worse at night. The expectoration is of a whitish color. Paroxysms of coughing at times caused vomiting, chiefly at night and very early in the morning.

The œdema of the legs has lasted two weeks and is no worse than when it began upon the third day of this relapse.

Bowels are irregular, and there is some increased frequency of micturition, especially at night.

Upon the day of admission (November 25th) he had chilly sensations and his temperature rose to 101.8°, falling to 97° at 8 A. M. on the 26th.

The physical examination showed that patient was anæmic, and a puffy condition of eyelids was noticeable. The pulse was of good volume but irregular in force and rhythm, with a suggestion of a collapsing quality. Rate 26 to quarter minute. The heart was found to be enlarged, the point of maximum impulse being in the fifth interspace, 8.5 cm. from mid-sternal line. A thrill was felt.

Upon auscultation, at the base of heart a short systolic murmur was noted, traceable to the anterior axillary line. Over body of heart a faint diastolic murmur was heard, becoming louder upon passing upwards and inwards. A friction rub was heard at the left of sternum in the second and third interspaces, and in the same situation to the right of sternum. At the aortic area a systolic murmur was quite

readily heard. Over the pulmonic area the heart-sounds had a loud rumbling quality and the second sound was markedly accentuated and reduplicated. The lungs showed the presence of a few moist râles at the bases. The presence of fluid in the abdominal cavity was made out. Œdema was marked in the feet and legs. There was no general glandular enlargement.

Upon the 30th he seemed more comfortable, but the cardiac conditions became more pronounced and the lungs presented evidence of congestion. And upon the morning of December 1st he was cyanotic and drowsy and had an annoying cough. The heart and lungs presented nothing new. Œdema was most noticeable in the tissues of face. Less urine was voided. At 8 P. M. he said he felt comfortable, but at 9.15 the nurse found him dead.

His blood was examined on day of admission and showed hæmoglobin 18 per cent, leucocytes 8600, red blood-corpuscles 1,768,000. On the 28th of November the leucocytes rose to 14,000, but upon the following day had fallen to 8000, whilst hæmoglobin rose to 31 per cent.

Examination of the urine on the day of admission presented the following condition: S. G. 1.013; reaction acid; much albumin present; sugar absent; many epithelial casts, pus-cells and small, round, nucleated cells present; a few red blood-cells noticed. Diazo-reaction absent. Albumin was present until the day of patient's death and was estimated upon several occasions to vary from .8-1.2 per cent.

Abstract from the Pathological Report.

Anatomical Diagnosis.—Acute ulcerative endocarditis of pulmonary valve; ascites; hydrothorax and hydropericardium; acute splenic tumor; small area of bronchopneumonia; glomerulo-nephritis; simple goiter; Meckel's diverticulum.

Autopsy by Dr. MacCallum, December 3, 1898. No. 1208. There was extensive œdema of the face, upper and lower extremities. The peritoneal cavity contained 600 cc. of slightly turbid fluid. Both pleural cavities contained excess of fluid.

The pericardial cavity contained about 200 cc. of a clear fluid in which floated a few flakes of coagulated lymph. Excepting over the right auricle, the serosa was smooth and glossy, here it was noticeably lustreless.

Heart.—Weight 400 grams. The right auricle and ventricle contain firm post-mortem clot. The tricuspid valves are delicate and competent. The pulmonary valves are the seat of a most extensive ulcerative endocarditis, two of its segments being almost completely destroyed, only tags with friable vegetations remaining; the third segment is better preserved and carries on its free margin a soft, friable, rather granular mass measuring $1 \times 2\frac{1}{4}$ cm. Aortic and mitral valves normal.

Spleen weighs 800 grams and measures $23 \times 13 \times 6$ cm. The organ is greatly enlarged and is attached by a few fresh slender adhesions to the body wall and stomach. Capsule generally thickened, but to a moderate degree only. Upon section the spleen is quite soft; color is dark purplish-red; the trabeculæ are well marked, and the Malpighian bodies are readily visible.

The kidneys are both alike. They are enlarged, weighing together 470 grams and measuring $12\frac{1}{2} \times 7 \times 4\frac{1}{2}$ cm. They are engorged with blood, œdematous and show all the typical signs of acute parenchymatous nephritis.

Bone-marrow of a femur is dark purple-red in color, soft but not diffluent.

The thyroid gland shows a moderate degree of goiter.

Lymph-glands generally are enlarged and firm.

The other organs are either normal or have no bearing in their pathological phenomena upon the special phase of disease under discussion.

Microscopic Examination.

Pulmonary Artery Valve.—One of the masses of vegetations examined shows that in its deeper parts it has been quite completely organized, but in its more superficial parts can be observed the presence of a dense mass of hyaline fibrin with a capping of more delicately fibrillated fibrin; more superficially are found small numbers of leucocytes.

The base of the valve is somewhat infiltrated.

Spleen shows great congestion. There is no evident increase in the other tissues. There is no especial accumulation of pigment.

Kidney section presents a few islands of connective tissue of small extent in the cortex. There are accumulations of small round cells about the blood-vessels and adjacent tubules. The tubules are dilated, the epithelium is degenerated and hyaline casts are numerous; many tubules contain leucocytes which sometimes invade the casts. The glomeruli are enlarged and completely fill the capsular space, and show a marked increase in the cells contained within the capillaries, and in some instances a fibrous thickening of the capillary walls is observable.

Bone marrow presents an increase of lymphoid cells. There is no fatty tissue evident.

Lymph-glands show an increase of polymorphonuclear leucocytes and an increase of the endothelium of the sinuses, with swelling of these cells.

Bacteriological Report.

At the time of autopsy cultures were made in plain agar, as it was only upon the following day that a suspicion arose of the possibility of gonorrhœal infection and no hydrocele fluid cultures were made. This latter procedure was, however, resorted to later.

The cultures from the vegetations and other sources proved negative on plain agar, excepting those from the lung and peritoneal cavity, which yielded respectively the Streptococcus pyogenes and the Staphylococcus pyogenes albus.

Within 24 hours of the autopsy cultures were made from the vegetations upon the valve in ascitic fluid agar, but upon examination these proved to be unfit for working out on account of contamination.

Coverslip preparations were made and examined from the vegetations and from the urethra. The former exhibited numerous diplococci sometimes within cells or amongst cell remains, but more often free. Their morphology corresponded closely to that of the gonococcus and they decolorized in Gram's solution. The latter preparation presented no definite micrococci.

Case 3.—Medical No. 9645. J. H. (colored), æt. 22, was admitted to the hospital upon March 9, 1899, complaining of pain and swelling in the right ankle.

Family history was negative.

Past History.—In childhood he had had mumps, measles and whooping-cough. He never had had rheumatism, typhoid fever, diphtheria nor scarlet fever. He had pneumonia about four years ago. He has no urinary disturbances, and denies gonorrhœa and syphilis, but admits exposure to both.

He does not use alcohol or tobacco.

Present Illness.—One evening four weeks ago he complained of soreness in the right ankle and next morning noticed the region much swollen. Following this he had for several nights chilly sensations and fever accompanied by herpes labialis, but with no night-sweats. He was treated outside for rheumatism.

At the present he complains of aching in all his limbs and especially of pain in the right ankle, which causes him to turn in bed with much difficulty. His ankle joint is swollen.

Physical Examination.—Patient looks ill. There is no cyanosis or herpes. Pressure over femoral artery gave a decided Corrigan impulse, and upon auscultation it gave a pistol-shot sound.

The heart was found much enlarged, the point of maximum impulse being in the fifth interspace 9 cm. from mid-sternal line. There was no thrill present.

Upon auscultation at apex, a loud systolic murmur, traceable far out into the axilla, was heard; likewise a soft blowing diastolic murmur. These could be traced readily upwards and inwards, and could be heard at the aortic and pulmonic areas and along both sternal borders. The second pulmonic sound was relatively accentuated. Pulse shows a fair volume and tension, collapses; rhythm regular and is 26 to the quarter minute.

Lung showed presence of a few coarse râles.

Abdomen and organs negative.

No general glandular enlargement.

Genitalia negative.

Legs show no œdema, no nodes, no scars.

Right ankle is a little swollen, sensitive to pressure, shows no effusion into joint.

March 10th, at midnight, vomiting set in and patient complained of abdominal pain. Pulse small, feeble and rapid. At 8 A. M. his temperature, previously normal, was found to be 100.8°, and the general condition improved considerably over what it had been during the night. But at 8.35 he died suddenly.

Blood Examination.—Leucocytes 55,000 upon day of admission.

Urine.—S. G. 1.011. It showed a few granular casts, epithelial cells and detritus; otherwise it was negative.

Medical bacteriological report upon March 9th proved that the blood culture made was sterile.

Abstract from Pathological Report.

Autopsy by Dr. Flexner, March 11, 1899. No. 1306.

Anatomical Diagnosis.—Acute endocarditis, perforation of aortic and mitral valves; purulent myocarditis; purulent and hæmorrhagic pericarditis; chronic passive congestion of the lungs; acute splenic tumor; anæmic infarction of spleen and kidneys; acute nephritis; cloudy swelling of viscera.

No œdema present.

Area of pericardium uncovered by lung tissue measures 10×10 cm. Upon opening the pericardial sac there is an accumulation of hæmorrhagic and purulent fluid about the great vessels at the base of the heart in the dependent portions of the sac dorsally. In all about 20 cm. of bloody fluid, containing many floating grayish-white purulent masses, can be obtained. The pericardial sac is adherent to the pleural surface of the left lung. The visceral layer of the pericardium is injected; the surface opaque, and there are yellowish adherent masses of fibrin and pus.

Heart weighs 400 grams.

The right and left auricles contain partially decolorized post-mortem clot. The tricuspid and pulmonary artery valves are apparently normal. The heart-wall is lax and the fibers well separated, and the myocardium of left ventricle shows pronounced fatty changes.

The aortic orifice above the valves measures 6 cm.

The Aortic Valve.—The right and middle segments of the valve appear delicate, and the left segment is neither retracted nor thickened, but has been perforated, apparently from below, in that there is a communication just above the base of the valve occupying the width of the right hemisphere of the segment, and measuring about 2 mm. Through this perforation there projects into the sinus of Valsalva a mingled red and white clot, the red portion being soft, the white dense and opaque. This clot almost fills the sinus and connects with a thrombus located upon and within the aortic segment of the mitral valve. This latter thrombus is situated upon the attached portion of the mitral valve, chiefly along the upper half. The valve has suffered a perforation at its base, so that the thrombus protrudes into the cavity of the left auricle. The endocardium of the left auricle above the valve bulges into the auricular cavity over an area 4 cm. sq., its elevation being 2-3 mm. There is no perceptible change in the endocardium itself. Upon incision of this diseased area one enters into a cavity in the substance of the heart-wall, which communicates with the thrombus covering the aortic and mitral valves. This valve [cavity?] contains necrotic and hæmorrhagic material, and at the left edge there is a distinct collection of pus. The cavity meas-

ures 2½ cm. in length and 1 cm. in depth; its walls are infiltrated and firm.

The spleen is enlarged and weighs 400 grams. It has no adhesions. Capsule delicate. In the mid-part of the ventricular surface is a pinkish infarction measuring $2 \times 1\frac{1}{2}$ cm. On section, the organ shows great increase of splenic pulp, consistence is somewhat reduced and the Malpighian corpuscles are visible. The infarction, upon cutting into it, is found to extend inwards for 1½ cm. into the splenic tissue; its consistence is firm.

The liver is congested and cloudy.

Kidneys.—The left one is large. The capsule strips off easily. There is a single anæmic infarction about ½ cm. in diameter, and lies quite superficially. Upon section the cortex is swollen and opaque; the glomeruli are visible and pink in color; striæ are coarse. Thickness of cortex is 8 mm. Resistance is lessened and the organ is œdematous and presents small hæmorrhages in the pelvic mucosa. The right organ is the same in all respects as the left, except for a larger anæmic infarction, measuring 10×12 mm., and a smaller one about the size of a hemp-seed. There are several punctate hæmorrhages in the kidney substance. Combined weight of kidneys is 400 grams.

The Right Ankle-joint.—The periarticular tissues are apparently normal, and the joint contains no excess of fluid, and the synovial membrane is perfectly smooth.

The remaining organs present nothing of significance.

Microscopical Examination.

The heart-muscle is œdematous.

The epicardium is likewise œdematous and thickened, showing an extensive proliferation of blood-vessels constituting a granulation tissue. Upon the surface of this tissue are some remains of epithelium, and here and there a thin, fibrinous deposit. Another section taken through the area of suppuration contains a fibrinous coagulum with many fragments of nuclei; underlying this is a loose granulation tissue infiltrated with leucocytes.

(No sections were made through either of the affected valves, as the heart was preserved as a museum specimen.)

Spleen.—The organ is gorged with blood which spreads apart the splenic elements. One end of the section shows an area of necrosis of splenic tissue sharply marked off by a zone of hæmorrhage with a fibrinous network, inside which is a bluish zone of fragmented nuclei of leucocytes.

Kidney.—Cells of tubules are disintegrated and ragged, showing no nuclei. Some tubules are packed with such desquamated cells.

The glomeruli show no extensive changes. There is no increase of interstitial tissue anywhere.

There are extensive accumulations of polymorphonuclear leucocytes found chiefly in the interstitial tissue, but often, too, in the tubules. Occasional small masses of plasma and round cells are seen in the medullary portions.

There is congestion of the capillary vessels.

Bacteriological Report.

Recognizing the possible gonorrhœal origin of the heart lesion, cultures were made upon what at the time was thought to be human serum, as well as upon plain agar, from the vegetations and infarcted areas of spleen and kidney. All endeavors to isolate the gonococcus failed, and this may be explained by the later discovery that by inadvertence ox-blood serum had been used instead of human serum. From the agar-plates the following organisms were isolated:

(*a*) Streptococcus pyogenes from vegetations on aortic and mitral valves, sinus of Valsalva, lung and renal infarct.

(*b*) Staphylococcus pyogenes aureus from vegetations on aortic valve, sinus of Valsalva and lung.

(*c*) Bac. proteus vulgaris from vegetations on mitral valve and sinus of Valsalva.

Cultures from heart's blood, liver, spleen, right ankle-joint and pericardium proved sterile.

Coverslips were from the vegetations on aortic and mitral valves, pericardial fluid, right ankle-joint, infarctions in spleen and kidney. Examination showed that in the vegetations there could be seen large numbers of large diplococci with some single or tetrad forms situated chiefly outside of leucocytes, only scattered polymorphonuclear leucocytes were found containing diplococci or groups of diplococci. The organisms readily decolorized by Gram's method of staining.

The pericardial fluid demonstrated the presence of vast numbers of polymorphonuclear, lesser numbers of large mononuclear and a few small mononuclear leucocytes, amongst which, after very careful searching, could be found a few polymorphonuclear cells containing small groups of diplococci within their protoplasm. These diplococci were larger than ordinary pus cocci, were biscuit-shaped and decolorized by Gram's method. Other coverslip preparations proved negative.

With these statements presented, it is clearly proven that the first case is one of undoubted gonorrhœal origin. But it must be conceded that in the two latter cases the lack of clinical evidence of a recent gonorrhœa, and the failure to demonstrate the presence of gonococci in culture rather weakens the assumption of their being gonococcal in nature.

Yet from the demonstration on coverslip preparations from the material of the valvular vegetations of micrococci, coinciding in all respective non-cultural characteristics with those of standard descriptions of the gonococcus, and, from the peculiar massive formation of the vegetations themselves, we regard it as reasonable that both cases should, without much doubt, be considered as examples of gonorrhœal endocarditis.

Discussion.

A review of the literature since the publication of Thayer & Lazear's article (Journal of Experimental Medicine, January, 1899) shows the following cases:

***Sears* (Medical & Surgical Reports, Boston City Hospital) reports a case in which, following several attacks of gonor-**

rhœa, the last attack five months before, the patient, a man aged 23, began to complain of pain in the back, stomach, and limbs, which gradually became more severe. The temperature was elevated from 99.5° F. to 105° F. Examination disclosed a harsh systolic murmur over the pericardium. As the disease progressed, the spleen became enlarged, and finally the pulse irregular and weak with marked cyanosis present. Death occurred on the seventh day after admission to the hospital. Autopsy showed an ulcerative mitral endocarditis, with rupture of the valve segments, infarcts in the left ventricle, spleen and kidneys, and on bacteriological examination a coccus was found quite generally distributed and unlike the ordinary pus cocci. No cultures were taken.

Sears also states that of a hundred and sixty-seven cases of gonorrhœal rheumatism admitted to the Boston City Hospital between the years 1880 and 1897, twenty-five showed cardiac murmurs to which no cause other than gonorrhœa was assignable.

Harbitz (Deutsch. med. Wochenschrift, 1899, XXV, pp. 121-124), in a study of forty-three cases of infectious (*i. e.* caused by organisms, streptococci, gonococci, etc.) endocarditis, found two in which organisms decolorizing by Gram's method, resembling gonococci in other respects, and not growing on the ordinary media (agar, serum, bouillon, gelatin), were found on the affected valves.

Jaccoud, in a clinical lecture on gonorrhœal endocarditis (Journal de Médecine Intern., Paris, 1900, IV, pp. 513, etc.), mentions seventeen cases of gonorrhœal endocarditis, his own and those he has collected for two years, in which the diagnosis was confirmed at autopsy. In four of these gonococci were found on coverslips from the valves, and in the remainder the history pointed clearly to it and autopsy showed ulcerative endocarditis, though no mention is made of what was found bacteriologically. In one of these cases gonococci were found on the valves, and, moreover, the myocardium was altered.

Karagcosganz (Eshenedelnik, 1899, No. 46) reports the case of a man, aged 24, who when first seen complained of epididymitis and fever. Examination showed elevation of temperature, anæmia, and a marked systolic murmur over the pericardium. The heart was not enlarged. The spleen was enlarged, and, towards the end of the disease, was four fingers' breadth below the costal margin. The temperature was remittent in character, and there were chills and sweats. The patient had had no disease previously, except intermittent fever. Two years before he contracted gonorrhœa which had never been thoroughly cured, and occasionally showed exacerbations. Death occurred after an illness of one month. Autopsy showed friable yellowish vegetations of the aortic valve, with destruction of the valve segments. No bacteriological examination was made.

Berg (Medical Record, April, 1899) reports the case of a man who, after an attack of gonorrhœa, had involvement of the metacarpo-phalangeal joint of the left thumb, accompanied by chills and elevation of temperature. When first admitted the patient gave evidence of an acute infection, with enlargement of the spleen, but without cardiac involvement. During the course of the disease, however, in which the symptoms became progressively worse, chills, vomiting and finally convulsions, supervening. Signs pointing to pyelo-nephritis and finally endocarditis at the mitral valve, set in, and death followed shortly thereafter. During the course of the disease, repeated examinations of the blood for malarial organisms and several Widal reactions all proved negative.

Cultures from the blood were also taken twice during life, in both instances proving negative.

Autopsy showed acute ulcerative endocarditis of two segments of the aortic valve with vegetations, two small vegetations on one of the flaps of the mitral valve, acute pyelonephritis, acute splenic tumor with one small splenic infarct, acute and chronic parenchymatous nephritis.

Microscopically, diplococci, decolorizing by Gram, were found in the vegetations from the aortic valve, and a few decolorizing diplococci in the fluid from the pelvis of the kidney. No cultures were taken.

The following case is reported by Loeb (Deutsches Archiv für klinische Medicin, 1899, XXV, pp. 411-420). The patient, a man aged forty-one, consulted him for swelling and pain in the right fore-arm. Three weeks before he had had an urethral discharge, but, with the exception of rheumatic pains in the lower extremities, he had otherwise been healthy. During the course of the trouble, which at this time was mild, pleurisy and swelling of the ankle developed, and about two weeks later cardiac signs and symptoms, consisting at first of a soft systolic murmur, but shortly afterwards of loud blowing murmurs at all the cardiac orifices, with both systolic and diastolic murmurs in the mitral area. Higher temperature, chills, and enlargement of the spleen followed and were followed in turn by signs of hypostatic pneumonia and adherent pericardium. Death occurred shortly thereafter. At autopsy the layers of the pericardium were found bound together by friable adhesions. The left heart was somewhat dilated but not hypertrophied. Hard calcareous vegetations, attached to the posterior and right anterior segments of the aortic valve, and projecting into the ventricle, were found. The segments themselves were found thickened and perforated. The remaining valves were unaffected.

The lungs were œdematous but showed no infarcts.

The spleen was enlarged and showed an infarct about the size of a hazelnut.

The kidneys showed change, and there was a small red infarct in the right.

The bladder was negative.

From the vegetations on the affected valve large numbers of diplococci, morphologically similar to gonococci, and decolorizing by Gram's method, were found. Bacteriological examination of the affected synovial sacs and joints and the splenic infarct were negative. No cultures were taken.

A most interesting case is reported by Bjelogolowij (Bolnitche Gazette, Bolkina, January, 1899, No. 4). The patient, a man aged 32, without history of inflammatory rheumatism or other disease except syphilis, was admitted complaining of palpitation and weakness of the heart and swelling of the right testicle, following gonorrhœa of one and one-half months' duration. According to the history the cardiac trouble had come on about two weeks before, and the epididymitis, which it proved to be, was of only a few days' standing.

On physical examination cardiac dulness was found somewhat increased, and at the apex two well-marked murmurs were heard, both being well transmitted. The pulse was collapsing in quality.

Course.—At first the course of the disease was mild, but after several days chills, fevers, sweats, with weakness, vomiting, diarrhœa, pericardial pain and enlargement of the spleen came on, ending finally in the patient's death in collapse.

Autopsy. Anatomical Diagnosis.—Verrucose endocarditis of the tricuspid valve; ulcerative endocarditis of the aortic valve; catarrhal pneumonia; chronic hyperplasia of the spleen; hæmorrhagic infarcts of the spleen; cyanotic induration of the liver; hæmorrhagic infarction of the kidneys; catarrhal colitis; catarrhal enteritis.

Heart.—The pericardium contained several tablespoonfuls of a serous, transparent, yellow fluid. Fibrinous blood-clots were present and a little fluid blood. The walls were pale, of a gray-red color and looked normal. On the upper surface of

the tricuspid valve there were several soft, wart-like excrescences, of a reddish color, and about the size of a grain of corn.

The two posterior cusps of the aortic valve were fused, disfigured and thickened with yellowish excrescences, which were covered on the surface with a friable and readily removable mass. The sinuses of Valsalva were dilated. The right cusp had a perforation the size of a goose-quill, filled with a bloody, fibrinous clot.

The mitral valve was normal.

Lungs.—Fibrinous pleurisy was present. Lungs otherwise negative save for a broncho-pneumonia at base.

Spleen.—Double its normal size, dark-colored, dense, trabeculæ well marked, and presenting on the lower aspect at the edges a hæmorrhagic infarct the size of a hazelnut.

Liver.—Normal, yellowish-red color, full-blooded.

Kidneys.—Large, capsules strip with difficulty; the cortical layer of each kidney thickened and contains a discolored hæmorrhagic infarct the size of a pea. The tissue is darker than normal and there is pus present in the pelvis of each kidney.

The mucosa of the bladder, beyond being pale, seemed normal.

The stomach and intestines were normal save for a catarrhal colitis.

The knee and ankle joints showed no change.

Phimosis was present. From the fossa navicularis a small drop of pus was expressed.

The testicles were without apparent change.

During life examination of the blood was made in the following ways with these results:

1. Slide of blood, stained with methylene-blue and eosin, showed apparently diplococci, but this is doubtful.

2. A small drop of blood from the finger planted on gelatin and peptone-agar gave no growth.

3. One cc. of blood was obtained, under aseptic precautions, from the vein at the elbow, and three plates, consisting of two-thirds glycerin-agar and one-third hydrocele fluid, were successively inoculated.

After forty-eight hours over twenty whitish, punctate colonies developed on the three plates. In some of these a darker center was noticed.

Microscopically, diplococci, resembling gonococci and decolorizing by Gram, were found.

Transplantation on gelatin-agar and on bouillon gave negative results.

Transplantation on an hydrocele-agar slant gave a slowly developing, beautiful growth, resembling that of the gonococcus in all respects, and proving the presence of gonococci in pure culture in the blood.

After death bacteriological examination gave the following results:

1. About twenty-four hours after death culture from the heart's blood made on hydrocele-agar gave negative result.

2. Tubes of agar, bouillon, gelatin and hydrocele-peptonglycerine-agar were inoculated with material obtained from the vegetations of the aortic valve; all with negative result.

3. Microscopical examination of the material from the vegetations of the aortic valve showed, however, diplococci completely identical with those found during life in the blood. These occurred both intracellular and extracellular, and decolorized by Gram.

4. No organisms were found microscopically on section of the splenic infarct.

NOTE.—Since the foregoing article has gone to press, a fourth case has come under our notice in the Pathological Laboratory.

Autopsy No. 1630 ——. There was a clear clinical history of an acute gonorrhœal urethritis, for which the patient had come to the dispensary for treatment. At the end of a week he disappeared, but returned in three months complaining of having had rheumatism of the joints, and pains in the chest and feeling generally unwell. He was at once admitted to the hospital under Dr. Osler's care, where his heart was found to be seriously involved. He died that night.

The autopsy showed an acute ulcerative endocarditis of the aortic valve, similar in character to that mentioned in Cases II and III. In coverslip preparations made from the vegetations micrococci were found having all the characteristics, morphologically and tinctorially, of Neisser's gonococcus. Owing to an unavoidable lapse of time and to over-much handling of the heart, cultures proved an absolute failure on account of resulting contamination.

N. MACL. H.
W. M. D.

AN EXPERIMENTAL STUDY CONCERNING THE RELATION WHICH THE PROSTATE GLAND BEARS TO THE FECUNDATIVE POWER OF THE SPERMATIC FLUID.

BY GEORGE WALKER, M. D.,

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In order to elucidate more clearly the connection which the prostate gland holds to fertilization, I have instituted a series of experiments in which the gland in white rats was excised in part and in whole, and its effects on fecundity noted.

Steinach, in a series of investigations made to determine the function of the seminal vesicles, found that by an excision of them the breeding property was reduced about one-half. When both prostate and vesicles were removed, it was brought down to nil. He did not excise the prostate gland alone, and could therefore adduce no proof as to the part it played.

Rats were selected on account of the ease with which the gland could be removed, and also from the minimum amount of danger of injuring the seminal ducts; the two being in rodents quite distinct, and not connected. The gland consists of four, or sometimes six, distinct lobes; the two anterior ones are very much larger than the others; are pear-shaped, and stand well up and away from the urethra, being held by a fascia connected with the bladder. They communicate with the urethra by several small ducts which empty into the roof of the lumen just in front of the vesicle neck. The posterior lobes are somewhat triangular in shape, are more closely connected with the urethra, and

are very much smaller and flatter, forming about one-fourth of the whole gland. They extend slightly around the ejaculatory ducts, and well up on the side of the urethra. The two lateral lobes are only occasionally present, and seem to be developed from the posterior ones. A second glandular substance is connected with the inner side of the seminal vesicles, and presents the same macroscopic appearance as does the prostate; but on microscopic section it is shown to be a structure similar to that of the vesicles.

The excision of the glands was done thus: The animals were etherized, the abdominal wall was carefully shaved and cleansed, and an incision made in the median line. This brought the anterior lobes into view, and by gently pulling the bladder forward and upward, they could very plainly be seen. They were very carefully separated from the bladder and from each other; a ligature was thrown around each, near the urethra, and both lobes excised; the posterior ones were exposed by pulling the bladder and seminal vesicles over the pubes; they were then very carefully separated from the surrounding structures and teased by a pair of small forceps from their connection with the urethra. This occasioned only slight bleeding, which soon ceased without a ligature. The abdomen was closed by interrupted silk sutures, the skin in the same manner, and the wound dressed with cotton and collodion. The animals usually made a rapid recovery, and appeared very lively on the following day.

The rats selected for operation were full grown, well developed, and in good physical condition. In several series the two anterior lobes were excised, and the effect on procreation noted. In the other series, all of the gland was removed, and the result also recorded.

The first series consisted of seven pairs; these were mated, and the number in the litter carefully noted. The two anterior lobes were then removed, and after sufficient recovery they were again mated.

Pair No. 1. Mated July 10th. Five weeks later the female gave birth to eight young; anterior lobes excised, and after recovery again mated August 22d; September 15th, a litter of eight was found.

Pair No. 2. Previously mated, and gave birth to ten young; two anterior lobes removed, and second mating August 21th. After two months, negative result.

Pair No. 3. Previously mated; five young. Anterior lobes excised and paired August 15th. Six weeks afterwards, four young.

Pair No. 4. Previously mated; eight young; removal of anterior lobes, and mated August 18th; after seven weeks, two young.

Pair No. 5. Previously mated; seven young. Anterior lobes excised, and second mating August 21st; after seven weeks, eight young.

Pair No. 6. Previously mated; eight young; anterior lobes excised, and mated second time August 23d; negative result.

Pair No. 7. Previous mating resulted in eight young; removal of anterior lobes; second mating August 30th; negative result.

From the above it is seen that in two pairs the breeding was normal; in two others the number was reduced to two in one case, and to four in the other, while in the remaining three the result was entirely negative.

A second series of fifteen pairs was taken; no previous mating, however, being done, as it had been ascertained by watching several other series that rats are fertile in nearly every instance. As in the preceding series, only the anterior lobes were removed; after complete recovery they were paired with the females.

Pair No. 1. Positive result after five weeks; eight young.
Pair No. 2. Positive result after six weeks; seven young.
Pair No. 3. Positive result after six weeks; eight young.
Pair No. 4. Positive result after five weeks; five young.
Pair No. 5. Positive result after eight weeks; ten young.
Pair No. 6. Positive result after nine weeks; eight young.
Pair No. 7. Positive result after four weeks; six young.
Pair No. 8. Positive result after six weeks; seven young.
Pair No. 9. Positive result after five weeks; five young.
Pair No. 10. Negative result after three months and twenty-five days.
Pair No. 11. Negative result after three months and twenty-five days.
Pair No. 12. Negative result after three months and twenty-five days.
Pair No. 13. Negative result after three months and twenty-five days.
Pair No. 14. Negative result after three months and twenty-five days.
Pair No. 15. Negative result after three months and twenty-five days.

Afterwards the males were killed, and the seat of excision examined. In three of the fertile ones it could be seen that a small amount of the anterior lobes had been left, while in the others it had all apparently been taken away. In the ones which had proved unfertile, there was no part of the anterior portion present. In quite a number of them, and most notably marked in the ones which had proved fertile, the posterior lobe had increased in size. In the negative ones no such increase in size was apparent.

A third series of animals was selected and mated before operation. The ones which bred were chosen for the excision of the gland. At the first operation only the anterior lobes were removed; they were again mated, and the fertile ones selected and subjected to a second operation in which all of the gland was taken away. The result is as follows:

Pair No. 1. Mated before operation; bred five. March 1st, removal of anterior lobes. Second mating March 5th. April 10th, bred three. April 12th, removal of the remaining gland; again mated; negative result.

Pair No. 2. Previous to operation bred eight; removal anterior lobes March 1st; mated March 4th; negative result. Second operation, entire removal April 10th; negative result.

Pair No. 3. Before operation bred four. First operation February 18th; mated March 3d. April 3d, bred seven. Second operation April 24th; entire removal. Mated April 26th; negative result.

Pair No. 4. Before operation bred seven; operation, removal anterior lobes March 1st; mated March 3d; April 22d, bred four. Complete removal April 24th; mated April 26th. After six weeks, positive result; bred six.

Pair No. 5. Before operation bred six; removal anterior lobes March 1st; mated March 3d; April 15, bred six. Second operation May 7th; complete removal; negative result.

In the above series, four out of the five were fertile after the first operation; number two being negative after the first and after the second. In two the number was normal, but in the remaining two pairs, the number was decreased in one case from five to three, and in the other from seven to four. In one pair, however, number three, it was increased from four to seven. After the second operation, four out of the five were sterile, only one bred.

The autopsies showed in the four barren ones that the gland had been entirely removed, whereas in the fertile ones, about three-fourths of the posterior lobes had not been excised.

In order to determine whether the seminal ducts had been injured during operation, and thus had prevented the outflow of the seminal fluid, a careful examination of both orifices and canals was made; they were found in each instance to be patent; moreover, on gently squeezing the seminal vesicles the secretion freely oozed through the orifices, and on stripping the vasa deferentia, the secretion freely exuded from the openings. The fluids thus obtained were examined microscopically and found to contain spermatozoa.

A fourth series of eleven pairs was selected, and the entire gland removed at one sitting. These, after recovery, were mated, with the result below recorded. It should be noted that the females had been kept for a long time separate, so that it was made sure that no fertilization was present.

Pair No. 1. After sufficient length of time proved negative.

Pair No. 2. Negative.

Pair No. 3. Negative.

Pair No. 4. Negative.

Pair No. 5. Negative.

Pair No. 6. Negative.

Pair No. 7. Negative.

Pair No. 8. Negative.

Pair No. 9. After six weeks, positive result; three young.

Pair No. 10. After seven weeks, two young.

Pair No. 11. After five weeks, five young.

It will thus be seen that in the eleven cases, eight were entirely negative, and in the remaining three, there was not a full litter in any instance; five being the nearest approach to it; in the other two the litter being two and three respectively.

The autopsies of Nos. 1, 2, 3, 4, 5 and 6, showed a complete removal of the gland; No. 7 presented a small piece of the lateral lobe; No. 8 showed only a slight trace of the left lobe; No. 9 showed fully three-fourths of the posterior lobes present, and a moderately sized stump of the anterior ones; in No. 10 there was found a large lateral lobe which had not been excised. In No. 11, although a positive result was obtained, there was apparently no gland left, either posterior or anterior. This last case was the only example in the whole series in which the male had proved fertile with no portion of the gland remaining.

The examinations proved that in most of the negative pairs there had been a complete removal of the gland; in two cases, however, some of it was present, while in the fertile ones, two presented large remnants of the gland which had failed to be excised; in one instance, all had apparently been removed. A similar examination as to the patency of the seminal ducts was made, and in only one instance was an occlusion found, and in that it was in only one duct. The others were perfectly open, and emitted their secretion.

The sexual desire and capacity of the rats were carefully noted both in those in which a partial excision, and in those in which a complete excision had been done. The examination was made by carefully watching them for some time each day after they were mated, subsequent to the operation. In every instance, the males were as sexually active after the operation as before; and in no instance was the capacity diminished.

The animals in which a complete removal of the prostate gland had been done were kept from four to seven months after the operation in order to ascertain whether any effect had been produced on the testes by the removal of the gland. At the end of this time the animals were killed with chloroform, and the organs carefully removed and examined. In every instance they were of normal size, of natural consistency, and in no way did they differ from the usual type. They were preserved in Zenker's fluid, and the subsequent microscopic sections did not reveal any changes.

In order to determine whether any effect was produced in the development of the testes by a very early removal of the prostate gland, I selected a certain number of young and healthy males, just at the age when the gland was beginning to develop; another series of about the same age being kept as controls. The prostate glands in the first number were entirely excised; the animals were kept for nearly six months, by which time they were thoroughly grown. They were then killed, and the testes upon examination were found to have developed normally; and they presented the same appearance and feel as were present in the other series of rats which were kept as controls. These were also examined microscopically, and no difference was found in them. The seat of the operation was examined; in one there had been a partial development of the gland; in the others no trace of it was discernible.

SUMMARY.

First series of seven pairs; anterior lobes excised; two bred normally, two had small litters, two were negative.

Series No. 2. Fifteen pairs; anterior lobes removed; nine bred normally, five proved negative, one escaped.

Series No. 3. Five pairs; after first operation, removal of anterior lobes; four out of five bred normally; one was negative. After a second operation where complete removal was done, one bred normally, four were negative.

Series No. 4. Eleven pairs; complete removal of the gland at one sitting; eight were negative, three had small litters; none positive.

Series No. 5. Prostate gland removed in early life, did not have any effect on the subsequent development of the testes.

Conclusions.

From the above experiments, the following conclusions can safely be drawn:

First. That a removal of the anterior lobes of the prostate gland in rats has no effect on breeding; but in a certain number it diminishes the fecundating power; and in a few it is destroyed entirely.

Second. Complete excision has a very marked effect on fecundity, reducing it to almost nil when the gland is entirely removed.

Third. Partial or complete removal of the prostate has no effect upon the sexual desire and capacity.

Fourth. Complete removal of the gland in the adult animal has no effect on the histological structure of the testicles. Complete removal of the prostate in the young animal has no effect upon the subsequent development of the testes.

SUMMARIES OR TITLES OF PAPERS BY MEMBERS OF THE HOSPITAL AND MEDICAL SCHOOL STAFF APPEARING ELSEWHERE THAN IN THE BULLETIN.

Charles Russell Bardeen, M. D. Casto-Vertebral Variation in Man.—*Anatomischer Anzeiger*, November 7, 1900.

Simon Flexner, M. D. Nature and Distribution of the New Tissue in Cirrhosis of the Liver (Preliminary Communication).—*Proceedings of the Pathological Society of Philadelphia*, November, 1900.

William Osler, M. D. An Address on John Locke as a Physician.—*Lancet*, London, October 20, 1900.

Howard A. Kelly, M. D. A Rapid and Simple Operation for Gall-Stones Found by Exploring the Abdomen in the Course of a Lower Abdominal Operation.—*Medical News*, December 22, 1900.

Henry J. Berkley, M. D. Clinical Cases. VII. The Pathology of Chronic Alcoholism.—*The American Journal of Insanity*, January, 1901

FURTHER OBSERVATIONS ON EPINEPHRIN.

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Shortly after the publication of my last paper on epinephrin,[1] I began to try simpler methods for the isolation of this substance, methods which should avoid the process of benzoating and the subsequent hydrolysis in the autoclave. Although the highly active bisulphate that was secured by these simpler methods was considerably contaminated with cholin and with compounds of the xanthin series, these attempts nevertheless taught me that the autoclave product as formerly described differs in several important particulars from that obtained without benzoating or subsequent hydrolysis. The latter product, which I might term unaltered or native epinephrin, is not precipitated by ammonia and fails to give many of the alkaloidal reactions which are characteristic of the autoclave product.

At first glance it might appear that the epinephrin hitherto described by me was a mixture of two different substances, one of which is precipitable by ammonia; the other, a physiologically active, pyrocatechin-like substance, not possessing this property; and this is in fact the view taken by v. Fürth[2] in a paper in which he comments on my results. This author, using a modification of the earlier methods of Holm[3] and Krukenberg[4] precipitates epinephrin with ammonia and a lead or zinc solution, suspends the resulting precipitate in methyl alcohol and decomposes it with concentrated sulphuric acid.

In this way he obtains a methyl-alcohol solution of a sulphate which has not been subjected to hydrolysis, and since it differs in several important particulars from epinephrin as described by me, he concludes that we are dealing with two different substances. He considers the term epinephrin to be applicable to a substance that is physiologically inactive, precipitable by ammonia, devoid of chromogenic properties, incapable of reducing silver nitrate or of forming a compound

[1] Zeitschr. f. physiol. Chem., Bd. xxviii, s. 318.

[2] Zeitschr. f. physiol. Chem., Bd. xxix, s. 105.

[3] Journ. f. pract. Chemie, Bd. c (1867), s. 150.

[4] Virchow's Archiv, Bd. ci (1885), s. 542.

with ferric chloride, while he applies the name suprarenin to the well known chromogen or physiologically active substance which in its native condition is non-precipitable by ammonia, reduces silver nitrate, yields an iron compound of specific qualities, fails to give a series of alkaloidal reactions characteristic of hydrolyzed epinephrin, and on fusion with potassium hydrate yields no odor of indol or skatol. Such, in brief, according to v. Fürth, are the main characteristics of what he calls two different substances.

I propose in this paper to take up the main points presented by v. Fürth and I hope to show that differences of method are alone responsible for the variations he has noted. What v. Fürth calls suprarenin is native or unaltered epinephrin.

I. PRECIPITATION BY AMMONIA.

Epinephrin obtained by hydrolyzing its benzoyl compound is precipitable from an aqueous solution by ammonia in the form of yellowish-white flocks which rapidly darken on exposure to the air and which are physiologically inactive. And here it may be remarked that complete precipitation of a salt of epinephrin is attended with some difficulty. The fractional method must be used in order to avoid an excess of ammonia, and toward the end of the operation, when only a little of the chromogenic substance remains, it is necessary to concentrate the solution with the help of the vacuum desiccator before the final precipitation is made. The various precipitates may be washed with ice-water, although it must be borne in mind that prolonged washing will dissolve almost all of the flocculent precipitate with the exception of a small amount of a dark insoluble residue which has become oxidized by long exposure to the air. When the fractional precipitation has been properly conducted the final filtrate from a solution of epinephrin bisulphate, for example, will contain nothing but ammonium sulphate, while on the various filters will be found all of the chromogenic substance.

Now, epinephrin, the chromogenic substance of the suprarenal gland, whether isolated by v. Fürth's or any other method that does not involve hydrolytic treatment, becomes immediately precipitable by ammonia as soon as such hydrolytic treatment is applied. Proof for this statement is found in the following facts:

1. The iron compound of "suprarenin" was prepared according to v. Fürth's method, which I consider a distinct contribution to our knowledge of the subject. His directions were followed with the exception that the compound was redissolved and reprecipitated out of acidulated methyl alcohol in order to remove as far as possible impurities that might be present. I then made benzoyl and acetyl epinephrin from this iron compound, and on saponifying these derivatives in the autoclave, I found that the resulting solutions yielded flocculent, inactive epinephrin on the addition of ammonia; in other words, they behaved exactly like compounds of the same name formerly described by me.

2. By cautiously adding ammonia to the methyl alcohol solution from which v. Fürth prepares his iron compound, I removed all excess of sulphuric acid and then drove off the methyl alcohol in the water bath. The residue was now taken up in water, filtered and heated in the autoclave for two hours in the presence of a little sulphuric acid and under a pressure of four atmospheres. The solution, which at first gave no precipitate with ammonia, now yielded an abundant flocculent precipitate on the addition of this reagent. Furthermore, I dissolved the iron compound in methyl alcohol containing a little acetic acid and removed the iron by repeated treatment with hydrogen sulphide. After evaporation of the methyl alcohol the residue was taken up in water, a little dilute sulphuric acid was added and this solution was hydrolyzed as before. Here again, the same result was obtained. The solution, which before treatment in the autoclave gave no precipitate with ammonia, now yielded epinephrin in abundance.

3. It might be asserted that the above facts are capable of another interpretation, that the substance which on hydrolysis yields this flocculent precipitate is not the chromogenic substance of the suprarenal capsule but an entirely different body which on precipitation drags down the chromogenic substance with it; that it is in fact merely present in v. Fürth's iron compound as an impurity. But my experiments with the active bisulphate of epinephrin, which can be converted quantitatively into this flocculent substance (barring small losses by conversion through oxidation into an insoluble form), fully prove that a separation of this body into a chromogenic and a non-chromogenic substance is impossible. It is itself, as stated in my earlier papers, an inactive modification of the active substance of the suprarenal gland. A further proof of this assertion is seen in the following: A chemist in the employ of one of our manufacturing firms has recently sent me about 1-10 of a gram of a micro-crystalline compound derived from the suprarenal gland that possessed a high degree of physiological activity and gave all the specific reactions of the native non-hydrolyzed form of the active principle. The method of its manufacture has not been made public and I have not as yet determined whether the compound represents the free base itself or some crystalline derivative.

This compound, which dissolves only sparingly in cold water, also fails to give a precipitate with ammonia unless subjected to treatment in the autoclave, behaving, therefore, like all specimens of the chromogen thus far isolated.

In short, it is an inherent property of the active principle of the suprarenal gland, prepared by whatever method, to fall out in the form of a flocculent, physiologically inactive precipitate on the addition of ammonia after previous treatment in the autoclave.

It is not surprising that v. Fürth should have failed to note this property of epinephrin inasmuch as he did not test any of my compounds as made by saponification of the benzoyl derivative, in respect to their precipitability by ammonia, but applied this test only to solutions obtained by decomposing his ammoniacal lead on ammoniacal zinc precipitates. The substance obtained by him from these solutions on the addition of ammonia is not epinephrin; it is either some de-

generate product of it or an entirely different substance. His observation that the active principle in its native state is not precipitable by ammonia is, however, entirely correct.

II. On the Iron Compound of Epinephrin.

Now that it has been shown that some of the properties of epinephrin, as heretofore described, are not inherent in the native substance but are developed by chemical manipulation, it is of interest to inquire into the behavior of its two chief modifications toward iron salts.

As before stated, v. Fürth has shown that a solution of the active principle in methyl alcohol yields a highly active precipitate on the addition of ferric chloride and ammonia, and that the addition of ferric chloride to a dilute aqueous solution containing a little acid gives a bright green color, while if the solution is alkaline, a carmine red color is the result.

Up to this time no analyses of this iron compound or of its derivatives have been given, nor are we informed whether its iron content varies on re-solution and re-precipitation, nor how far variability in this respect is affected by different modes of manipulation.

This author also appears to believe that the salts of epinephrin described in my previous papers are incapable of yielding an iron compound except as the chromogen is present as an impurity. But the experiments presently to be described show that epinephrin bisulphate is quantitatively convertible into an iron compound indistinguishable in appearance and chemical reactions from that described by v. Fürth, although differing in two respects from his compound: first, in that it can be precipitated directly from an acidulated aqueous solution of epinephrin, and second, that it is physiologically inactive. These differences, however, like others already alluded to, are due solely to differences in previous manipulation; in short, the conditions here are the same as in the case of the precipitation by ammonia, for if the methyl-alcohol solution from which v. Fürth derives his iron compound be taken and the methyl alcohol expelled, the residue dissolved in water, acidulated with a little dilute sulphuric acid and treated in the autoclave as already described, a transformation into what I have hitherto called epinephrin will be found to have occurred.

After removal from the autoclave the solution still possesses a high degree of physiological activity, but the addition of ferric chloride and ammonia now yields a precipitate, the iron compound of epinephrin, which is physiologically inactive. Here, too, the hydrolytic action of the autoclave is responsible for an inactive form of the iron compound, capable of precipitation out of acidulated aqueous solutions of the active principle.

Conversion of epinephrin bisulphate into an iron compound.

The following experiment was made with 1.197 grams of pure epinephrin bisulphate, another portion of which had served as the source of the phenylcarbamic di-ester of epinephrin described by me in an earlier paper.[5] The salt was dissolved in very dilute sulphuric acid, and ammonia was cautiously added until about two-thirds of the epinephrin was precipitated in two fractions in the form of yellowish-white flocks. These were repeatedly washed with ice water and the washings were added to the original filtrates. The flocculent precipitates were now separately dissolved in very dilute sulphuric acid and converted into an iron compound by the addition of ferric chloride and the subsequent addition of ammonia to very near the neutral point.

These precipitates were repeatedly washed by sedimentation in tall cylinders until the ammonium sulphate was entirely removed.

The compound was then redissolved in dilute sulphuric acid, reprecipitated with ammonia and washed as before, collected on a filter and dried over sulphuric acid.

The filtrates from the precipitations by ammonia together with the washings were also converted into the iron compound, which, after being washed in a tall cylinder by sedimentation, was redissolved in very dilute sulphuric acid, reprecipitated by ammonia and washed till all traces of sulphuric acid had disappeared.

In this connection it may be remarked that the washing of the iron compound as above described until it is free from ammonium sulphate and sulphuric acid is accomplished with difficulty. Large quantities of water are required and the amount of the iron compound which remains in solution in the supernatant fluids depends of course upon the reaction of these fluids. This reaction, I may remark, is difficult to maintain at the same level in the several cases. Usually the wash fluids were colorless, but even then the addition of ammonia caused a farther precipitation of the iron compound. It is to be noted, also, that the iron content of the compound here considered varies with the conditions of its precipitation. Thus, if the iron content of a given fraction is 8.50%, that precipitated from its washings may be as high as 12.62%, or even higher, and this same variability is met with if the portion on the filter is redissolved and reprecipitated. Whether this variability also attaches to the physiologically active iron compound obtained by the use of methyl alcohol has not yet been determined.

Briefly stated, the results of the above experiments are as follows: 1.197 grams of epinephrin bisulphate made from the benzoyl compound were treated with ammonia until the larger portion of the epinephrin was precipitated; this was washed with cold water and the washings added to the original filtrates. Both the flocculent free epinephrin and that which still remained as a bisulphate in the filtrates were converted into an iron compound. According to v. Fürth, only the filtrate and the washings from the free epinephrin could yield an iron compound. Yet after all the manipulations above described the following fractions of this iron compound were obtained:

[5] Amer. Journ. of Physiol., vol. iii, 1899–1900, No. 8, p. XVII.

From epinephrin, Precipitate I.	From epinephrin, Precipitate II.	From the filtrates from Precipitates I and II.
0.1412 gram.	0.2845 gram.	0.2438 gram.

From the washings of these precipitates further amounts of the iron compound were obtained and in relatively the same proportion in each case. These additional fractions, together with what was recovered from filter papers, cylinders and funnels, brought the total amount of the iron compound obtained up to 0.9242 gram. A small quantity, amounting to perhaps 0.02 gram was further precipitated from the washings of the last fraction and was not taken into consideration.

The object of the above experiment was to learn whether this compound can be as easily made from flocculent, inactive epinephrin as from its filtrates, but the fact which incidentally appeared, that notwithstanding the many manipulations involved, so large an amount as 0.9242 gram of an iron compound was obtained from the above-mentioned quantity of bisulphate, fairly warrants the statement that epinephrin bisulphate is quantitatively convertible into an iron compound.

In the case of the iron compound from epinephrin, Precipitate II. and from the filtrates from epinephrin, Precipitates I and II, like conditions of precipitation were maintained both in respect to the amounts of the reagents employed and the reaction of the wash fluids, with the result that the iron content of the two fractions was nearly the same. This is shown in the following table:

Iron compound from epinephrin, Precipitate II.	Iron compound from filtrates from epinephrin, Precipitates I and II.
0.1105 gm. burned on an ashless filter left 0.014 gm. Fe_2O_3 = 8.87 per cent Fe.	0.0965 gm. burned on an ashless filter left 0.0122 gm. Fe_2O_3 = 8.85 per cent Fe.
0.174 gm. burned in a current of oxygen, left 0.021 gm. Fe_2O_3 = 8.44 Fe.	0.1473 gm. burned in a current of oxygen, left 0.0189 gm. Fe_2O_3 = 8.96 per cent Fe.

The carbon and hydrogen content of the two fractions was also in fairly close agreement, but the analyses are reserved for consideration in a later paper in which I hope to give a fuller comparison of this compound and that made by v. Fürth in the manner already described. A single analysis of a specimen of the latter compound was made and it was found to contain 12.8 per cent of iron.

This higher iron content unaccompanied by other data affords no basis of comparison between the two substances; for, as we have seen, a fraction of my iron compound which contains 8.5 per cent of iron may by chemical manipulation have its iron content raised to over 12 per cent.

In conclusion, then, it may be stated that an active salt of epinephrin made by saponification from its benzoyl compound is convertible into an iron compound, both in methyl alcohol and in aqueous solution.

When made from an aqueous solution this iron compound is physiologically inactive, also less soluble in dilute acetic acid than v. Fürth's compound, but in respect to its chemical reactions it is indistinguishable from his compound.

By benzoating the iron compound of v. Fürth, trial experiments have shown me, that the entire series of derivatives formerly described by me may be obtained. From it I have also made the acetyl compound and by decomposing it in the autoclave I have obtained an active bisulphate indistinguishable in appearance and reactions from that formerly described by me.

Our compounds also agree in yielding, on the addition of moderately strong alkali, the volatile base of a coniinepiperidine-like odor so often noted in my previous papers.

III. Other Effects of Treatment in the Autoclave.

V. Fürth has also stated that the active principle of the gland as contained in the fluids prepared from his lead or zinc precipitates, yields no precipitates on the addition of certain alkaloidal reagents, as picric, phosphotungstic or tannic acid, iodine in potassium iodide or concentrated solution of zinc chloride.

It is, however, easy to prove that here, too, as in the instances relating to precipitability with ammonia and with ferric chloride, we are dealing with characteristics which only require appropriate treatment for their development. If the iron compound prepared according to the directions of v. Fürth is converted into the acetyl derivative and this is saponified in the autoclave, a solution is obtained from which the epinephrin bisulphate formerly described by me can be prepared without difficulty. Aqueous solutions of this salt readily give precipitates with the above-named alkaloidal reagents, while solutions which are derived from the material from which v. Fürth's iron compound is prepared, that is to say, from material which has not been exposed to hydrolysis, fail to give precipitates with these reagents.

A further instance of this behavior is furnished by the compound already alluded to as having been sent to me by the chemist of one of our manufacturing firms. Before treatment in the autoclave with dilute sulphuric acid this substance also yields no precipitate with such alkaloidal reagents as picric acid, phosphotungstic acid, iodine chloride or iodine in potassium chloride, but after such treatment a prompt precipitation occurs on the addition of these reagents.

IV. Skatol: A Decomposition Product of Epinephrin.

I have stated in previous papers that on fusing the chromogen of the gland with powdered potassium hydrate and then diluting with water the penetrating odor of skatol arises from the solution. When this solution of the fusion products was shaken with ether and the ether allowed to evaporate, little globules remained, having an intensely fæcal odor and giving the characteristic reactions of skatol with sufficient definiteness to warrant the belief that this substance is a decomposition product of the active principle under the conditions specified.

V. Fürth has failed to substantiate my statements in this particular, but the tests which I have made with the acetyl compound prepared directly from his own iron compound, as also with a specimen of epinephrin bisulphate prepared

from this acetyl derivative have still further convinced me that my statements were correct. In order to get olfactory evidence of the presence of skatol, it is only necessary to smelt about 0.1 gram of either of these compounds in a cautious manner with an appropriate amount of powdered potassium hydrate, the two reagents being spread out on the bottom of an Erlenmeyer flask, then to dilute with water, shake with ether, and evaporate the ether out of a Drechsel wash bottle with the help of a suction pump. The water contained in the ether is left behind as ice and the low temperature produced is an effectual bar to the complete escape of the skatol. On opening the wash bottle after the removal of the ether one obtains sufficient proof that skatol is present from its characteristic odor.

V. Analytical Considerations.

It would now be in order to give analytical data to illustrate the changes that occur in the autoclave and to show what relation obtains in respect to elementary composition between the autoclave product and its less manipulated, physiologically more active counterparts. But an accident that happened to me in my laboratory in the early days of December and which for nearly three months kept me from my laboratory has made more than an introductory discussion of this point impossible.

It would appear that the simplest method of arriving at a conclusion in regard to the extent of the analytical differences existing between epinephrin as made by the autoclave method and that made by avoiding this treatment, would be to analyze the acetyl derivative when made from v. Fürth's iron compound. The direct conversion of this iron compound into its acetyl derivative contends with the difficulty of purifying and washing the former substance in consequence of its amorphous character, and is also open to the suspicion that secondary changes, such as oxidation, may occur in the process of acetylizing. I have nevertheless converted this iron compound into its acetyl derivative, without first removing the iron. Preliminary analyses have shown that its nitrogen content varies from 4.18 to 4.28 per cent. My empirical formula, for triacetyl epinephrin as made by the autoclave method, calls for 3.31 per cent N. In the above instances the nitrogen content was determined by the method of Kjeldahl, and the observed deviation from the theoretical requirements are too large to bring the acetyl compound now under consideration into a simple relation with that formerly described by me.

It may be remarked in passing that the observed results vary still more widely from those found by v. Fürth, who gives 5.71 per cent as the average nitrogen content of his acetyl compound, while the theoretical requirement is either 5.81 or 5.86 per cent, according as the one or the other of his assumptions that the active principle is tetrahydrodioxypyridin or dihydrodioxypyridin is made the basis for the empirical formula.

At the present moment it is impossible to express, in analytical terms, the differences that exist between the epinephrin of my former papers and the somewhat less altered, native principle. Their qualitative differences and resemblances have been pointed out in this paper. While it is perhaps unwise to anticipate the results of future researches, I would suggest that one or more of the following chemical changes may possibly account for the differences that have been noted: 1. The saponification of the benzoyl derivative may not be a complete one; one benzoyl group may have been retained, in which case my epinephrin would represent the monobenzoyl derivative of the native principle. 2. Inasmuch as treatment in the autoclave of every form of the active principle, no matter how prepared, leads to the appearance of new properties, it is in order to ask whether the entrance of one or more molecules of water into the compound, or the loss of an atom of nitrogen in the form of ammonia or a combination of these two alterations, will not be found to lie at the bottom of the whole difficulty. In case one or both of these changes take place, they would of course also occur in the case assumed under 1. 3. It is also possible that the autoclave is responsible for a doubling of the original molecule after previous elimination of water and also of nitrogen in the form of ammonia or of a simple amine.

These and other points will constitute the subject matter of a future communication. The methods that have hitherto been employed by me have served their purpose in giving us unstable but characteristic derivatives of the native principle. These have retained a high degree of physiological activity and give all the known reactions of the native product, but they show, in addition to these, certain new reactions, such as precipitability by ammonia and by alkaloidal reagents.

In conclusion I would state that the autoclave is also responsible for a decrease in the physiological activity of the compound. This is shown by the data recently obtained by Prof. Reid Hunt[6] with a specimen of unaltered epinephrin bisulphate, which was prepared from v. Fürth's lead precipitate, by removal of the lead and subsequent fractional precipitation. Other methods of isolation in which also the use of the autoclave plays no part are now in progress in my laboratory, and detailed statements as to the composition and physiological activity of the resulting products will follow later.

[6] Amer. Jour. of Physiol., vol. v, No. 2, p. VII.

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In the methods of instruction especial emphasis is laid upon practical work in the Laboratories and in the Dispensary and Wards of the Hospital. While the aim of the School is primarily to train practitioners of medicine and surgery, it is recognized that the medical art should rest upon a suitable preliminary education and upon thorough training in the medical sciences. The first two years of the course are devoted mainly to practical work, combined with demonstrations, recitations and, when deemed necessary, lectures, in the Laboratories of Anatomy, Physiology, Physiological Chemistry, Pharmacology and Toxicology, Pathology and Bacteriology. During the last two years the student is given abundant opportunity for the personal study of cases of disease, his time being spent largely in the Hospital Wards and Dispensary and in the Clinical Laboratories. Especially advantageous for thorough clinical training are the arrangements by which the students, divided into groups, engage in practical work in the Dispensary, and throughout the fourth year serve as clinical clerks and surgical dressers in the wards of the Hospital.

REQUIREMENTS FOR ADMISSION.

As candidates for the degree of Doctor of Medicine the school receives:

1. Those who have satisfactorily completed the Chemical-Biological course which leads to the A. B. degree in this university.

2. Graduates of approved colleges or scientific schools who can furnish evidence: (a) That they have acquaintance with Latin and a good reading knowledge of French and German; (b) That they have such knowledge of physics, chemistry, and biology as is imparted by the regular minor courses given in these subjects in this university.

The phrase "a minor course," as here employed, means a course that requires a year for its completion. In physics, four class-room exercises and three hours a week in the laboratory are required; in chemistry and biology, four class-room exercises and five hours a week in the laboratory in each subject.

3. Those who give evidence by examination that they possess the general education implied by a degree in arts or in science from an approved college or scientific school, and the knowledge of French, German, Latin, physics, chemistry, and biology above indicated.

Applicants for admission will receive blanks to be filled out relating to their previous courses of study.

They are required to furnish certificates from officers of the college or scientific schools where they have studied, as to the courses pursued in physics, chemistry and biology. If such certificates are satisfactory, no examination in these subjects will be required from those who possess a degree in arts or science from an approved college or scientific school.

Candidates who have not received a degree in arts or in science from an approved college or scientific school will be required (1) to pass, at the beginning of the session in October, the matriculation examination for admission to the collegiate department of the Johns Hopkins University, (2) then to pass examinations equivalent to those taken by students completing the Chemical-Biological course which leads to the A. B. degree in this University, and (3) to furnish satisfactory certificates that they have had the requisite laboratory training as specified above. It is expected that only in very rare instances will applicants who do not possess a degree in arts or science be able to meet these requirements for admission.

Hearers and special workers, not candidates for a degree, will be received at the discretion of the Faculty.

ADMISSION TO ADVANCED STANDING.

Applicants for admission to advanced standing must furnish evidence (1) that the foregoing terms of admission as regards preliminary training have been fulfilled, (2) that courses equivalent in kind and amount to those given here, preceding that year of the course for admission to which application is made, have been satisfactorily completed, and (3) must pass examinations at the beginning of the session in October in all the subjects that have been already pursued by the class to which admission is sought. Certificates of standing elsewhere cannot be accepted in place of these examinations.

SPECIAL COURSES FOR GRADUATES IN MEDICINE.

Since the opening of the Johns Hopkins Hospital in 1889, courses of instruction have been offered to graduates in medicine. The attendance upon these courses has steadily increased with each succeeding year and indicates gratifying appreciation of the special advantages here afforded. With the completed organization of the Medical School, it was found necessary to give the courses intended especially for physicians at a later period of the academic year than that hitherto selected. It is, however, believed that the period now chosen for this purpose is more convenient for the majority of those desiring to take the courses than the former one. The special courses of instruction for graduates in medicine are now given annually during the months of May and June. During April there is a preliminary course in Normal Histology. These courses are in Pathology, Bacteriology, Clinical Microscopy, General Medicine, Surgery, Gynecology, Dermatology, Diseases of Children, Diseases of the Nervous System, Genito-Urinary Diseases, Laryngology and Rhinology, and Ophthalmology and Otology. The instruction is intended to meet the requirements of practitioners of medicine, and is almost wholly of a practical character. It includes laboratory courses, demonstrations, bedside teaching, and clinical instruction in the wards, dispensary, amphitheatre, and operating-rooms of the Hospital. These courses are open to those who have taken a medical degree and who give evidence satisfactory to the several instructors that they are prepared to profit by the opportunities here offered. The number of students who can be accommodated in some of the practical courses is necessarily limited. For these the places are assigned according to the date of application.

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